10

Benign Diseases of the Endometrium

Mark E. Sherman, M.D., Michael T. Mazur, M.D., and Robert J. Kurman, M.D.

Accurate histopathologic diagnosis is important in the management of benign endometrial conditions and lesions. Although many functional disorders do not produce specific morphologic changes, pathologic examination plays a critical role by excluding entities that do. Because the histopathologic appearance of the endometrium reflects a women's hormonal milieu, endometrial tissue studies may be useful in diagnosing abnormalities of the hypothalamic–pituitary axis or assessing the effects of exogenous hormones. The two main indications for endometrial biopsy or curettage are to elucidate the etiology of abnormal uterine bleeding or infertility. Basic clinical terms used to characterize abnormal uterine bleeding are summarized in Table 10.1. Readers may consult reviews

Table 10.1. Clinical characterization of abnormal bleeding

Oligomenorrhea	Infrequent bleeding (more than every 35 days)
Polymenorrhea	Frequent bleeding (less than every 21 days)
Hypomenorrhea	Decreased flow (regular periodicity)
Menorrhaghia	Excessive bleeding (amount and number of days)
Metrorrhagia	Irregular bleeding (amount may be normal or increased)
Menometrorhagia	Excessive, irregular bleeding (frequent and prolonged)

for an overview of the differential diagnosis.[25] This chapter considers benign, congenital, and acquired conditions involving the uterine corpus. For a more comprehensive discussion of the diagnosis of these diseases in endometrial biopsies and curettings, the reader is directed to texts that specifically address these issues.[166,316]

Congenital Abnormalities

Congenital abnormalities of the uterus are uncommon.[18] Many of these abnormalities are due to the effects of exogenous hormones, such as diethylstilbestrol (DES)[130] in utero or imbalances in endogenous hormones associated with abnormal gonads and chromosomal defects. The latter group of congenital disorders is described in Chapter 1, Embryology of the Female Genital Tract and Disorders of Abnormal Sexual Development, and the upper and lower genital tract structural abnormalities associated with in utero DES exposure are discussed in Chapter 4, Diseases of the Vagina. Genotypically normal females with normal gonads may also have müllerian duct abnormalities. These developmental aberrations, such as defects in the fusion of the müllerian ducts, are caused by errors in embryogenesis. The etiology of these developmental errors is unknown, but hormonal imbalances or genetic abnormalities may be involved. These disorders are frequently associated with malformations in the urinary system and the distal gastrointestinal tract (see Chapter 1). For practical purposes, these müllerian duct abnormalities can be divided into two categories: (1) abnormalities of fusion and (2) abnormalities caused by atresia.

Fusion Defects of the Müllerian Ducts

Normally, the upper one-third of the vagina and the uterus are formed by fusion of the paired müllerian ducts. After fusion, the intervening wall degenerates, forming to endometrial cavity and upper vaginal canal.[233] Nonfusion of the müllerian ducts results in uterus bicornis (Figs. 10.1c and 10.2). If the ducts fuse but the wall between the two lumens persists, an abnormal septate uterus results. If the defect is minor or confined to the fundus, the uterus is referred to as arcuatus (Fig. 10.1b). If the full length of the uterus and upper vagina is divided by a septum, the condition results in uterus didelphys with a partially double vagina (Fig. 10.1a). These congenital anomalies may cause infertility or spontaneous abortion and therefore require surgical correction.[97,290]

Atresia of the Müllerian Ducts and Vagina

Atresia of the müllerian ducts and vagina may be partial or complete. The etiology of these conditions is obscure, although a genetic cause is suggested in families with multiple affected siblings. The pattern of inheritance may be autosomal recessive or dominant.[304,305] If just one of the müllerian ducts is involved, only the fimbriae and a small muscular mass at the pelvic sidewall will form. Occasionally, a rudimentary structure remains as an appendage attached to the unaffected side, giving rise to what is referred to as uterus bicornis unicollis with a rudimentary horn (Fig. 10.1d). With bilateral atresia, the upper genital tract may consist of bilateral noncanalized standards of muscular tissue located on the lateral pelvic walls. In Rokitansky–Kuster–Hauser syndrome, a severe defect characterized by müllerian and vaginal aplasia, patients may have urinary tract anomalies such as a pelvic kidney or anephria. Vertebral and other skeletal abnormalities may also be present, suggesting a more generalized morphogenetic abnormality.

Patients with these conditions are endocrinologically normal and develop normal gonads. Lindenman and colleagues have postulated that activating mutations affecting the gene coding for antimüllerian hormone or its receptor may be related to the development of this syndrome.[154] If the anomaly is associated with obstruction of the vagina and func-

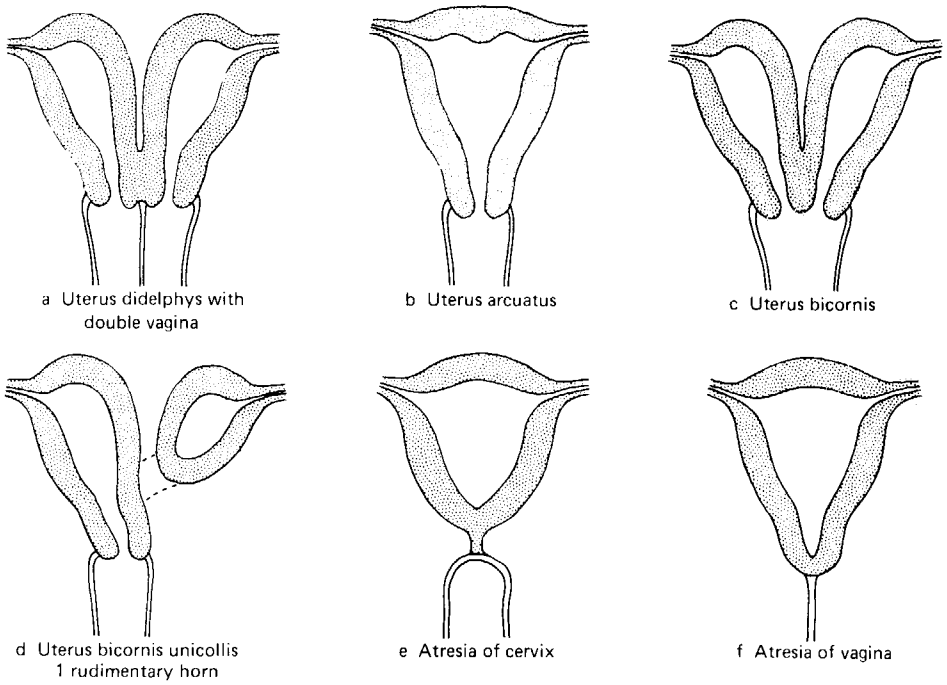

Fig. 10.1. Schematic representation of the main congenital abnormalities of the uterus and vagina. These abnormalities are caused by persistence of the uterine septum or obliteration of the lumen of the uterine canal. (Reprinted by permission of Salder, ref. 233.)

tional endometrial tissue is present, hydrocolpos may be present at birth, or patients may present with primary amenorrhea. A uterus bicornis unicollis may develop in women with one affected müllerian duct, resulting in a pelvic mass and cyclic pelvic pain associated with menses. A number of multiple malformation syndromes have been associated with müllerian or vaginal agenesis. Winter syndrome, a genetically inherited autosomal recessive disorder, is characterized by vaginal agenesis, renal agenesis, and middle ear anomalies.[305] Treatment of patients with complete vaginal atresia requires surgery to create a neovagina. If the anomaly is isolated vaginal atresia (Fig. 10.1f), as most commonly occurs, the patient usually will be fertile if a normal uterus and fallopian tubes are present.

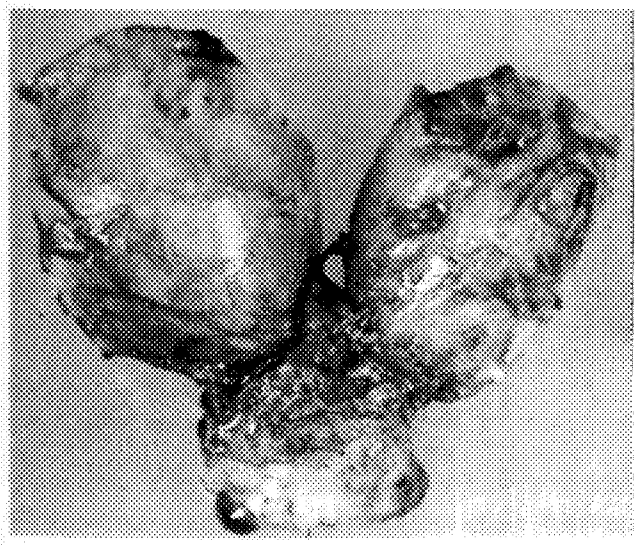

Fig. 10.2. Bicornuate uterus. The specimen is unopened.

Inflammation

Endometritis is histopathologically classified as *acute or chronic* depending on the type of inflammatory cells present; however, these designations do not necessarily reflect the duration of disease. In some cases of endometritis, a specific etiologic agent or a distinctive inflammatory pattern (e.g., granulomatous) can be recognized, whereas in others the findings are nonspecific. The diagnosis of endometritis is sometimes challenging because specific types of leukocytes are present in normal endometrium in defined distributions that vary with menopausal status and the phase of the cycle.

Normal Hematopoietic Cells of the Endometrium

Immunohistochemical studies have demonstrated that B lymphocytes are present mainly in aggregates in the basalis and are rarely found in the functionalis.[32] Occasional lymphoid follicles can be found in otherwise normal endometria.[207] T lymphocytes

are relatively uncommon in the proliferative phase but increase during the secretory and menstrual phases.[32] CD 44, an adhesion molecule that may be involved in lymphocyte homing, was detected in all four midsecretory and 9 of 11 late-secretory endometria in one study.[310] Granulated lymphocytes with the phenotype CD 2+, CD 3− may be found in predecidual tissue that is present in mid- and late-secretory endometrium. Formerly, these cells were designated as endometrial stromal granulocytes.[31,135] In addition, polymorphonuclear leukocytes (PMNs) are present in small numbers throughout the cycle but do not become evident in large numbers before the tissue breakdown and necrosis associated with menses occurs.[214] In contrast to lymphocytes and PMNs, plasma cells are not normally present in the endometrium. Rare mast cells demonstrable with toluidine blue staining may be found in the endometrium, primarily within the basalis. Mast cells are also found in the myometrium, endometrial polyps, and leiomyomas.[54] The number of mast cells present in the endometrium and myometrium tends to decrease with advancing age. The significance of mast cells in the development of endometrial pathology has not been established.[54]

Acute and Chronic (Nonspecific) Endometritis

Although the cervix acts as a barrier to the entry of microorganisms into the endometrial cavity, most types of endometritis result from ascending infection. Endometritis related to bacteremia or secondary spread to the uterus from a primary salpingitis (e.g., tuberculosis) is unusual. During menses, abortion, parturition, and instrumentation (curettage, insertion of an intrauterine device, cervical conization), the cervical barrier to infection is breached, allowing normal vagina flora access to the endometrial cavity, but colonization and infection are uncommon. A study analyzing the histologic findings in the endometrium of women with documented upper genital tract infection (UGTI) and laparoscopically confirmed acute salpingitis suggests that classification of endometritis into "acute" and "chronic" forms based on the type of inflammatory infiltrate may not be valid.[137] This study found that the endometria of women with acute salpingitis usually did not contain large numbers of PMNs in the stroma. In fact, PMNs comprising at least 30% of the inflammatory cells occurred in only 27% of the cases. PMNs were found in the superficial endometrium, but numerous lymphocytes and plasma cells were identified in the stroma. Therefore, these women would have been classified histopathologically as having chronic endometritis. Possibly, these patients may have had acute salpingitis superimposed on an occult low-grade, chronic endometritis.

Clinical Features

Clinically significant *acute endometritis* is usually associated with pregnancy or abortion. The complex clinical aspects of postpartum and postabortal endometritis are described elsewhere.[148,177] Most acute endometritis is caused by hemolytic *Streptococcus*, *Staphylococcus*, *Neisseria gonorrhoeae*, and *Clostridium welchii*.

Pathologic Findings

Chronic endometritis has been observed in 3–10% of women undergoing an endometrial biopsy for investigation of irregular bleeding.[98,228] Patients may have menometrorrhagia, mucopurulent cervical discharge, uterine tenderness, or an elevated erythrocyte sedimentation rate and/or leukocytosis, but some women are asymptomatic. Chronic endometritis has been associated with an abortion in 41%, with salpingitis in 25%, with an intrauterine device in 14%, and with a recent pregnancy in 12%.[34] It also is associated with necrotic tissue, such as an infarcted polyp or carcinoma, or cervical stenosis secondary to radiation or cryosurgery. Endometritis associated with pregnancy and abortion is characterized by an acute inflammatory infiltrate. Based on a study of 111 women with cervical in-

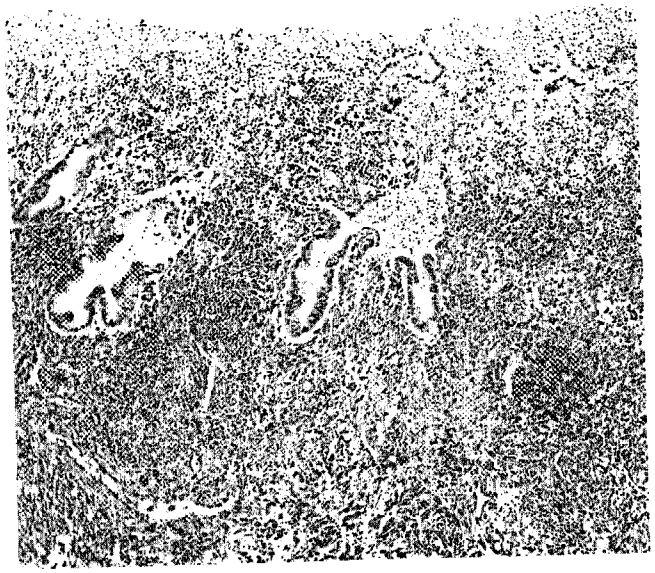

Fig. 10.3. Acute endometritis. A profuse infiltrate of polymorphonuclear leukocytes destroys and fills gland lumens. A microabscess is present on *right*.

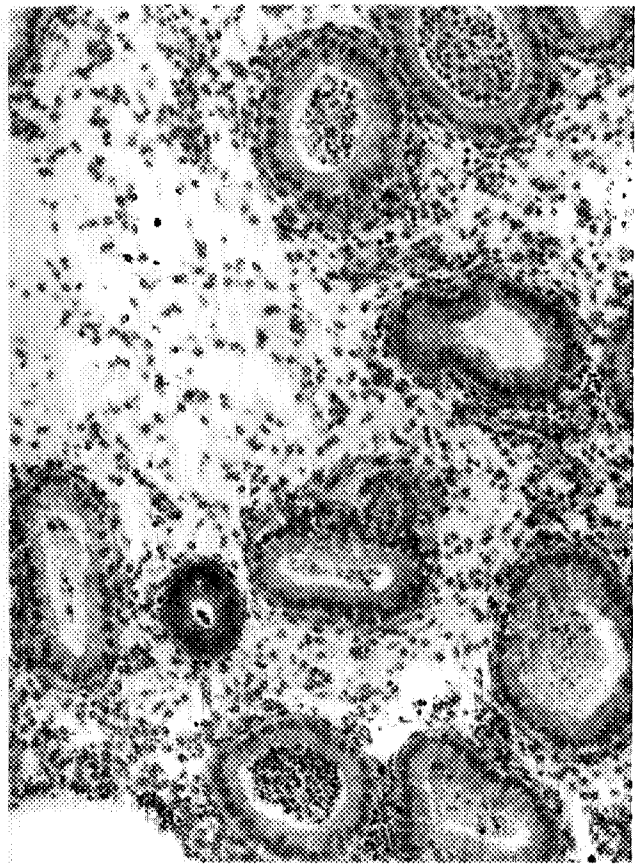

Fig. 10.4. Endometrial glands with luminal debris. Tubular glands near the surface contain neutrophils and debris in the lumens. There was no evidence of endometritis in the specimen. This change should not be misinterpreted as acute endometritis.

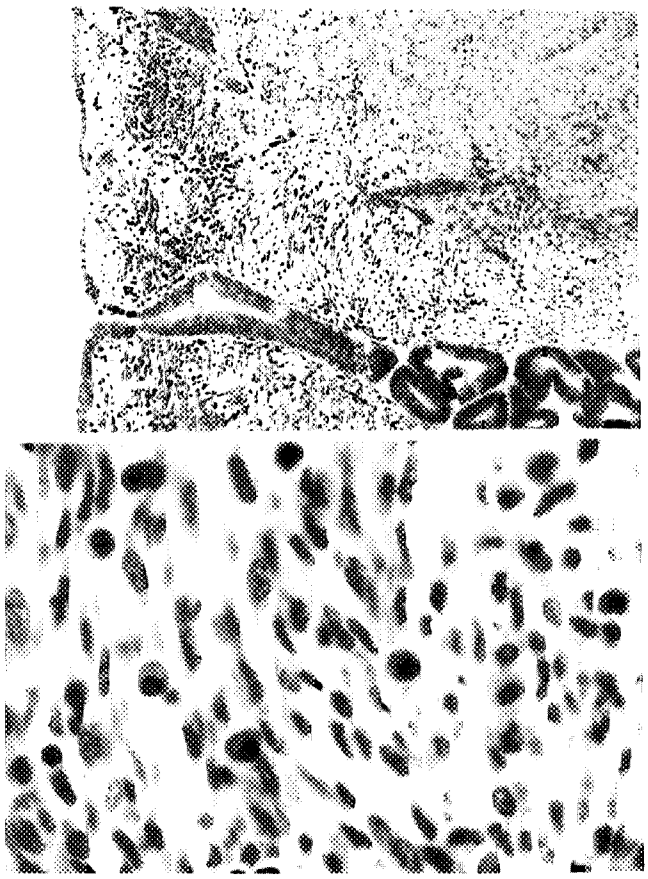

Fig. 10.5. Chronic endometritis. *Top*: Chronic endometritis characterized by aggregates of lymphocytes and plasma cells. *Bottom*: Plasma cells with eccentrically placed nuclei and clockface chromatin pattern.

fections caused by gonorrhea, *Chlamydia*, or bacterial vaginosis and 24 controls, Korn et al. reported that women with proliferative endometrium had a fourfold increased risk for having signs of upper genital tract disease. The authors postulated that hormonal effects or loss of barrier function after menses may render the endometrium susceptible to infection.[140]

Currently, identification of a specific microorganism is based on culture. Criteria for the histologic diagnosis of acute endometritis include identification of moderate to large numbers of PMNs in nonbleeding endometrium, aggregates of PMNs in the stroma, (microabscesses) or filling and disruption of glands by PMNs.[214] These findings must be distinguished from necrosis, hemorrhage, and infiltrates of PMNs occurring as a normal physiologic event in menstrual endometrium (Fig. 10.3). Occasionally, isolated glands in otherwise normal endometrium contain PMNs and debris (Fig. 10.4), reflecting entrapped menstrual detritus. This focal findings is not diagnostic of acute endometritis, which is typically a diffuse process.

The diagnosis of chronic endometritis rests on the identification of plasma cells, but lymphocytes, macrophages, and rare PMNs may be present (Fig. 10.5).[28,34,72,228] Plasma cells may be difficult to distinguish from lymphocytes and endometrial stromal cells possessing an eccentric nucleus. Diagnostic plasma cells contain an eccentric nucleus with a characteristic clumped chromatin pattern and a paranuclear pale-staining area representing the Golgi apparatus. Routine use of special stains to identify rare plasma cells is not recommended, and examination under high magnification should be reserved for biopsies that are suspicious at low power. Specifically, spindle cell alteration of the stroma (Fig. 10.6) or secretory endometrium that is difficult to date should prompt closer study. The spindle cell alteration is characterized by a tendency of the endometrial stromal cells to palisade around glands in a pinwheel arrangement. The nuclei of the stromal

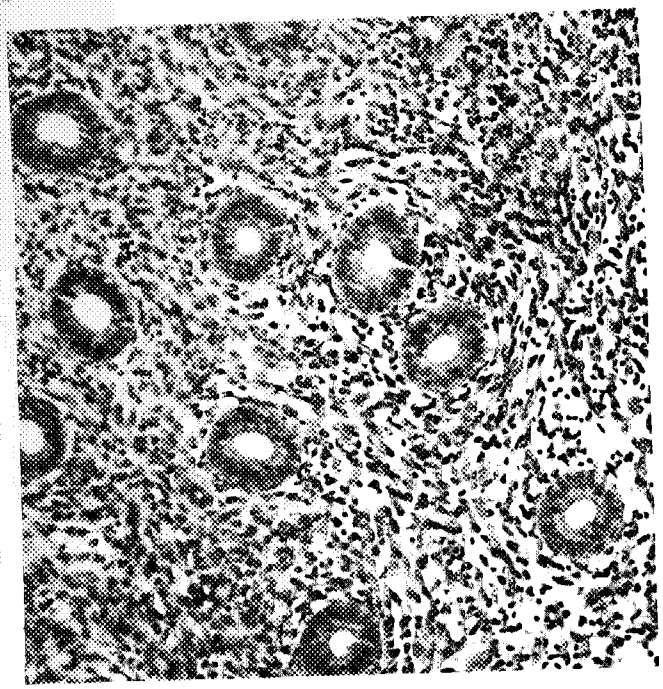

Fig. 10.6. Chronic endometritis. Note the spindle-shaped stromal cells surrounding glands in a pinwheel arrangement.

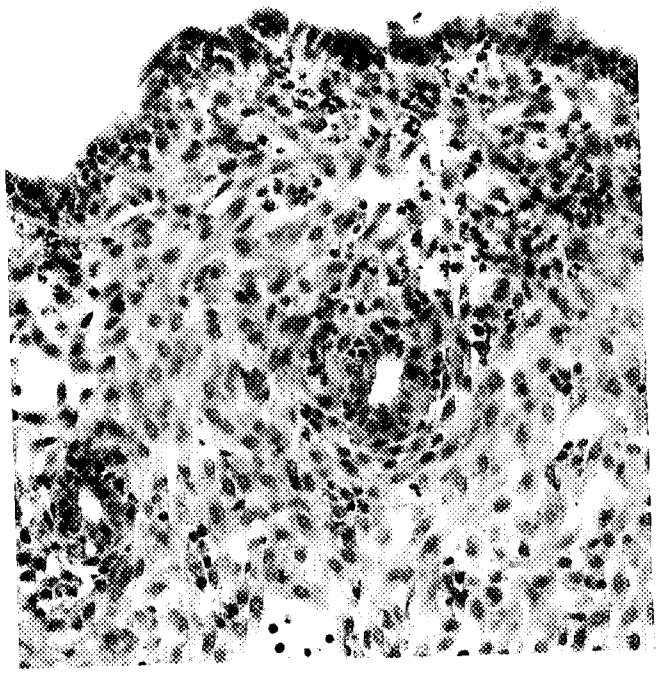

Fig. 10.7. Chronic endometritis. Numerous neutrophils in addition to lymphocytes are present involving the surface of the endometrium, glands, and stroma. Plasma cells were present elsewhere in the specimen.

cells may appear more elongated and slightly enlarged. Frequent problems with dating include glands and stroma that are not consistent with the same menstrual date, inactive glands that are difficult to classify as proliferative or secretory, and extensive fragmentation; the latter finding has been associated with *N. gonorrhoeae*.[137] Glandular cells may be stratified, with karyomegaly and prominent nucleoli, and both glands and stroma may show increased mitotic activity. Occasionally these cells may be identified in cervical cytology specimens, prompting an interpretation of atypical glandular cells of undetermined significance. Rarely, the surface epithelium in chronic endometritis shows squamous metaplasia.

One study of women with acute salpingitis and laparoscopically confirmed upper genital tract infection (UGTI) found that small numbers of plasma cells had low specificity for the diagnosis of endometritis.[137] In this study, identification of one or more plasma cells in the endometrial stroma per 120× field and five or more PMNs per 400× field in the surface epithelium (Fig. 10.7) had a sensitivity of 94% and a specificity of 85%, respectively, for the diagnosis of UGTI. The authors questioned the clinical significant of finding rare plasma cells in endometrial biopsies obtained from asymptomatic women because, in an unpublished series of 29 biopsies performed as part of an infertility workup, they found rare plasma cells in two women who had normal hysterosalpingograms and negative *Chlamydia trachomatis* serology. Korn et al. also demonstrated that the concordance between clinical findings diagnostic of endometritis, histopathologic plasma cell endometritis, and microbiologic detection of *N. gonorrhoeae* and *Chlamydia* was poor.[141] These authors also identified plasma cell endometritis in 2 (9%) of 11 controls, noting that the significance of this finding in women who do not meet standard diagnostic criteria is unclear. Accordingly, if chronic endometritis is diagnosed exclusively on the basis of the detection of extremely rare plasma cells, the cells in question should have typical morphology and the modifier "mild" may be added. Our understanding of the clinical significance of pathologic diagnoses of endometritis has been limited historically by our inability to use pathologic samples to identify and localize pathogens to endometrial tissue. It is hoped that these problems can be overcome with newer techniques.[267]

Clinical Behavior and Treatment

Chlamydia trachomatis and *N. gonorrhoeae* are the most common upper genital tract pathogens cultured from the endometrium, tubes, or cul-de-sac concurrently with the histopathologic diagnosis of chronic endometritis. Other less common isolates include *Escherichia coli*, *Streptococcus agalactiae*,

and *Peptostreptococcus magnus*.[137] Accordingly, endocervical cultures for gonococci and *Chlamydia* may be indicated after the histologic diagnosis of chronic endometritis is rendered. The histologic diagnosis of endometritis often is associated with pelvic inflammatory disease. In a study comparing endometrial biopsy, clinical examination, and laparoscopy in the diagnosis of acute pelvic inflammatory disease, Paavonen et al. found that a biopsy diagnosis of chronic endometritis was associated with acute salpingitis at laparoscopy in 89% of patients, whereas endometritis was confirmed in only 67% of women with an abnormal bimanual examination.[206] The association of mucopurulent cervicitis, endometritis, and salpingitis suggests that chronic endometritis may represent an intermediate stage of pelvic inflammatory disease between ascending cervicitis and salpingitis. The importance of the endometrial biopsy as a predictor of pelvic inflammatory disease is underscored by the observation that significant pelvic adhesions can be found at laparoscopy despite normal hysterosalpingography.[159] Because chronic endometritis may be found without salpingitis, it is conceivable that early endometritis can cause infertility.[206] Thus, the endometrial biopsy can serve as a method for directing specific therapy or indicating the need for laparoscopy.

Chronic Endometritis: Specific Types

Chlamydia

Clinical Features

Data from several Western European countries and the United States indicate that *C. trachomatis* infection, defined by culture or a high serologic antibody titer, is associated with 50–60% of cases of salpingitis.[104] The risk of infertility after an episode of salpingitis rises from 11% after one episode to 54% after three or more episodes.[297] Most patients undergoing tuboplasty for tubal stenosis or adhesions that appears to have an infectious etiology have never had pain, bleeding, or any clinical sign that would have suggested the diagnosis.[104] This finding suggests that *C. trachomatis*, possibly in association with other microorganisms, can cause an acute salpingitis or a chronic "silent" salpingitis that is recognized only during the course of an infertility workup.

Pathogenesis

Animal experiments have convincingly demonstrated that *C. trachomatis* by itself can cause salpingitis and tubal obstruction. In one study of 100 guinea pigs, unilateral salpingitis and pyosalpinx developed in all the animals following an inoculation of *C. trachomatis* into the tube.[238]

Pathologic Findings

Findings at surgery in women with culture-proven *C. trachomatis* include adhesions and a viscous effusion in the pouch of Douglas, shiny red peritoneal surfaces suggesting inflammation, and mesothelial cysts ranging from a few millimeters to macroscopic in size (see Chapter 17, Diseases of the Peritoneum). Cytologic examination of the peritoneal fluid reveals numerous lymphocytes and plasma cells and clusters of reactive mesothelial cells. The fallopian tubes can show a wide range of findings from acute to chronic salpingitis (see Chapter 14, Diseases of the Fallopian Tube). Chronic endometritis caused by *C. trachomatis* displays a mixed inflammatory infiltrate composed of plasma cells, lymphocytes, and PMNs (see "Acute and Chronic Endometritis"). One study has suggested that *C. trachomatis*-associated endometritis is associated with a denser plasma cell infiltrate than gonococcal endometritis.[137] In addition, lymphoid follicles containing transformed lymphocytes were found with *Chlamydia* infection but not with gonococcal infection. Similarly, in a study using immunohistochemistry to detect *Chlamydia*, the organism was found in only 4% of 90 endometrial biopsies showing chronic endometritis as compared to 57% in biopsies showing severe chronic endometritis and superimposed acute inflammation.[303] Chlamydial endometritis was associated with stromal necrosis and reparative cytologic atypia in the glandular and surface epithelium. Chlamydial inclusions were difficult to identify because of obscuring inflammation. In another study, *C. trachomatis* elementary bodies were identified by direct immunofluorescence in 75% of cases, and typical intracellular *Chlamydia* inclusions were found in more than 60%.[136] Stern et al. detected chlamydial DNA in only 1 of 43 samples tested using a sensitive technique, which prompted them to concluded that *Chlamydia* plays a limited role, if any, in mild or moderate endometritis.[267] Chlamydia has also been detected in 9 (11.7%) of 77 fallopian tubes showing chronic salpingitis using a polymerase chain reaction-based method in combination with enzyme immunoassay.[107]

Clinical Behavior and Treatment

Chlamydia cultures performed after a histologic diagnosis of chronic endometritis may facilitate early treatment, thereby minimizing the risk of tubal damage and infertility. Patients undergoing tuboplasty should be cultured and treated before microsurgery to improve the chances of successful intrauterine

pregnancy.[104] *Chlamydia* infections usually respond to tetracycline therapy.

Mycoplasma

Mycoplasma infection of the endometrium has been associated with infertility and fetal wastage.[28,279,280] Three species, *Mycoplasma hominis*, *Mycoplasma fermentans*, and *Ureaplasma urealyticum*, have been demonstrated in the lower female genital tract.[39,84,85,204,279] Most infections are transmitted by sexual contact, but the organisms have been cultured from prepubertal girls and women who have not reported sexual contact, suggesting that the anal canal or other sites may represent the source of infection in some cases.[72] Although mycoplasma species, especially *U. urealyticum*, may play a role in some cases of unexplained infertility, the relationship of this organism to endometrial infection is controversial.[39,40,99] Data regarding both the culture of the organism from the endometrium and the association of positive cultures with an inflammatory endometrial response have been conflicting.[39,40,99,112] The differences in isolated rates among infertile women may be due to cervical contamination because mycoplasmas frequently colonize the lower genital tract. However, Andrews et al. reported a threefold risk for endometritis in women undergoing cesarean section, which presumably permitted culture of placental tissue without cervical contamination.[7]

Significant endometrial infection with *U. urealyticum* should cause an identifiable inflammatory response. Horne et al. have described a lesion termed subacute focal inflammation (SFI) consisting of focal collections of lymphocytes, plasma cells, and rarely PMNs that they have identified in these patients.[112] The lymphoid aggregates characteristic of SFI are most easily identified in the secretory phase from the 20th to the 23rd days (postovulation day 6–9) of the cycle, when there is maximal stromal edema. The lymphoid aggregates generally lack germinal centers and tend to be localized immediately beneath the surface endometrium, adjacent to glands, or around spiral arterioles. Our experience with SFI is limited. The link between *U. ureaplasma* infection and infertility is not well understood and may be indirect. For example, in a study of 262 patients, 87% of women with SFI reportedly had laparoscopically detected pelvic adhesions compared to only 11% who did not have SFI ($p = 0.0001$).[33] One speculation is that ureaplasmas, if truly pathogenic, may act by producing adhesions or increasing the risk for developing more severe adhesions. Cervicovaginal isolation of *U. urealyticum* was associated with male factor infertility in one study, suggesting that the organism may produce more significant pathology in men, by interfering with spermatogenesis and reducing spermatozoa motility, rather than producing endometritis.[40]

Anaerobic Gram-Negative Rods

Anaerobic gram-negative rods, such as those associated with bacterial vaginosis, may represent endometrial pathogens. Studies evaluating the etiologic role of these organisms in endometritis have been hampered by difficulties related to assessing the frequency of vaginal colonization and bacterial vaginosis. Peipert et al. found that bacterial vaginosis was associated with a threefold risk of having laparoscopic, histologic, or microbiologic evidence of upper genital tract disease.[208] In contrast, Hillier et al. found that only recovery of gram-negative rods from the endometrium was associated with endometritis, whereas clinical bacterial vaginosis was not significantly associated in a multivariate analysis.[106] In addition, this study found agreement between species identified in the endometrium and the fallopian tube. Finally, Korn et al. reported that 10 of 22 patients with bacterial vaginosis had endometritis compared to only 1 of 19 controls.[139] Although further evaluation of the role of these organisms in upper genital tract infection is needed, accumulated data suggest a possible role.

Tuberculosis

Endometritis caused by *Mycobacterium tuberculosis* is a manifestation of a systemic disease; its frequency is proportionate to that of pulmonary tuberculosis in a population, but it is considerably more rare, with very low rates in most developed countries.[24,120,182,194,271] Tuberculous endometritis may be found in women of any age. Clinical presentation includes a pelvic mass, lower abdominal pain, and infertility. The diagnosis may not be made until a hysterectomy is performed and pathologic examination reveals typical caseating granulomas. The endometrium is the second most commonly infected site in the female genital tract after the fallopian tubes, and it is involved in one-half to three-quarters of patients with genital tuberculosis.[194] Endometrial involvement is generally secondary to seeding by organisms draining from an infected fallopian tube. Salpingitis in turn is usually secondary to hematogenous or, rarely, lymphatic spread from a primary infection in the lungs or gastrointestinal tract.[103] The extent of the inflammatory involvement in tuberculous endometritis varies from a focal

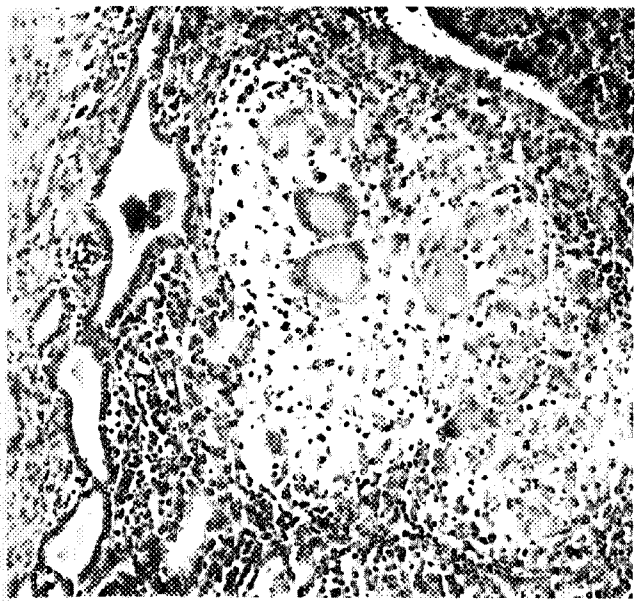

Fig. 10.8. Tuberculous endometritis. Tuberculous endometritis with a nonnecrotizing granuloma containing Langhans' giant cells.

process with very few granulomas to a diffuse process with ulceration of the mucosa and extensive caseous necrosis. Typical granulomatous inflammation with Langhans' giant cells (Fig. 10.8) may be present, but sometimes nonspecific endometritis with focal or diffuse infiltrates of plasma cells and lymphocytes and glandular microabscess is the only pathologic finding.[60]

The inflammation usually is confined to the superficial and intermediate portion of the endometrium, with transmural involvement occurring only in very severe infections.[194] As with any severe inflammatory process, the epithelium may show reactive proliferative changes with cellular stratification, mild nuclear atypia, and squamous metaplasia that mimic a neoplastic process. Histologic diagnosis of tuberculosis is difficult because granulomas are often focal and take up to 2 weeks to develop, and the functionalis, where granulomas usually occur, is shed every 4 weeks.[194] Thus, if tuberculosis is suspected, a curettage, rather than an endometrial biopsy, should be performed during the late-secretory or menstrual phase of the cycle. Specific diagnosis requires culture or identification of acid-fast organisms, because other microorganisms and noninfectious processes may be associated with granulomatous inflammation. Acid-fast bacilli are rarely demonstrated, even when cultures are positive.[194] Patients with tuberculous endometritis are nearly always sterile because they also have severe tubal infections. After appropriate antimicrobial therapy, granulomas become hyalinized, but the inflammatory infiltrate may persist for years. In fertile patients there is a high risk of tubal implantation, and intrauterine pregnancy may terminate in fatal miliary tuberculosis.

Sarcoidosis

Granulomatous endometritis has been reported in patients with *systemic sarcoidosis*.[108,277] In contrast to tuberculosis, granulomas in sarcoidosis are typically noncaseating and acid-fast bacilli are not identified. Because classic caseating granulomas may not be identified in tuberculous endometritis and identification of organisms may be difficult, patients with granulomatous endometritis must be carefully evaluated.

Fungal Infections

Blastomycosis (*Blastomyces dermatitidis*)[75] and coccidioidomycosis (*Coccidioides immitis*)[101,236] may produce granulomatous endometritis as part of a disseminated infection. There have been case reports of mycotic infection consistent with *Candida*[225] and cryptococcosis (*Cryptococcus glabratus*)[212] in the endometrium. The Gomori silver-methenamine and periodic acid–Schiff (PAS) stain are helpful for identifying these organisms.

Viral Infections

Herpes simplex virus (HSV),[2,73,95,222,241] *cytomegalovirus* (CMV),[63,167,293] and *human immunodeficiency virus* (HIV)[211,306] are known to infect the endometrium. Human papillomavirus (HPV) infection of the endometrium is controversial. In a study that used a combination of polymerase chain reaction (PCR) and in situ methods, HPV DNA was not detected in normal endometrium but was identified in endometrial carcinomas, as has been previously reported.[202]

Both acute[2,95,241] and latent[222] HSV infection have been reported. Acute herpes endometritis may result from an ascending infection or a disseminated viremia.[2,73,241] In acute herpes infection, the glandular cell have ground glass nuclei that are enlarged and contain round eosinophilic inclusions surrounded by a halo. There are associated patchy necrosis, acute inflammation, and multinucleated giant cells.[73,241] In latent herpes infection, immunohistochemistry may demonstrate HSV-specific virion and nonvirion antigens.[222] The clinical significance of "latent" infection is unknown. HSV-1 and HSV-2 were also identified in 13 (72%) of 18 cases of en-

dometritis in HIV-infected women as compared to 2 (11%) of 18 HIV-negative controls.[306]

Cervical cultures detect CMV infection in about 14% of women during pregnancy.[179] In contrast, CMV represents an unusual incidental microscopic finding in nonpregnant healthy women.[293] CMV endometritis has been reported in immunocompromised women with systemic CMV infection[26,237] and as a primary infection in nonimmunocompromised patients.[167] CMV may infect the endometrium during pregnancy and may be linked to spontaneous abortion.[73] Because of its occult presentation, the frequency of CMV infection of the endometrium is probably underestimated. CMV infection is characterized by an inflammatory infiltrate composed of lymphocytes and plasma cells. The endometrial epithelial cells are markedly enlarged and contain large, round basophilic nuclear and cytoplasmic inclusions (Fig. 10.9). CMV DNA has also been detected in paraffin blocks using the polymerase chain reaction in a case of chronic endometritis with ill-defined nonnecrotizing granulomas but without any of the other features of CMV infection.[83] The patient had systemic CMV infection and CMV in the endocervix. The Arias–Stella reaction (see Chapter 9, Anatomy and Histology of the Uterine Corpus) may be confused with CMV because both lesions show marked nuclear enlargement. In the Arias–Stella reaction, however, cells typically display a hobnail arrangement and cytoplasmic vacuolization, associated with luminal secretions and changes consistent with gestational endometrium (i.e., decidua). CMV endometritis lacks these features and typically is associated with a plasma cell infiltrate.

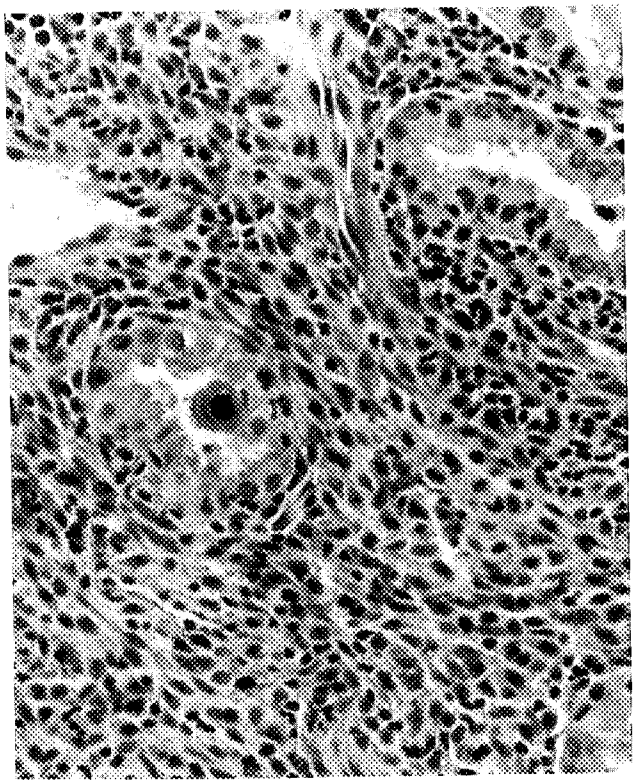

Fig. 10.9. Cytomegalovirus endometritis. An enlarged glandular cell contains a large, round, basophilic inclusion.

HIV has been detected using immunohistochemistry and in situ hybridization within cells demonstrating monocyte/macrophage differentiation located in endometrial stroma.[211] In a study comparing 12 endometrial samples from HIV-infected women to matched controls, HIV-infected patients with menstrual symptoms showed an increase in lymphocytes (CD 45) and T cells (CD 3), prompting the suggestion that nonclassical forms of chronic endometritis may be common in advancing HIV disease.[123]

Parasitic Infections

Schistosoma,[20,181,301] *Enterobius vermicularis*,[239] and *Echinococcus granulosus*[291] are rare causes of endometritis in the United States, but *schistosomiasis* is endemic in Central America, Africa, the Middle East, and the Far East. Patients usually present with amenorrhea and infertility. The infection may be mild or severe and is characterized by granulomatous inflammation with lymphocytes, plasma cells, eosinophils, and histiocytes closely simulating a tubercle. The endometrial surface may ulcerate and be replaced by granulation tissue. Diagnosis is made by identifying the ova in tissue sections or in smears of vaginal secretions. Toxoplasmosis (*Toxoplasma gondii*)[219,268] evokes a nonspecific inflammatory reaction in the endometrium. The microorganism can be identified by immunofluorescence. Fragmentary data implicate this organism in the endometrium as a cause of congenital toxoplasmosis and habitual abortion.

Xanthogranulomatous Inflammation

There have been several reported cases of *xanthogranulomatous or histiocytic endometritis*.[29,30,231,247] The lesion involves the endometrium, but may extend into the myometrium, and is characterized by an extensive accumulation of foamy histiocytes. The condition has been reported in postmenopausal women, some of whom have been radiated previously for endometrial or cervical carcinoma. Presentations include vaginal bleeding, vaginal discharge, cervical stenosis, and pyometria. It has been suggested that the lesion results from obstruction as-

Fig. 10.10. Xanthogranulomatous endometritis. Large numbers of endometrial stromal cells with foamy cytoplasm. Lymphocytes and plasma cells also are present.

sociated with hematometria, inflammation, and perhaps some factors specifically related to radiation-induced tumor necrosis, such as the generation of free radicals and lipid peroxidation.[231] Microscopically, xanthogranulomatous endometritis is characterized by numerous histiocytes with foamy, glandular, or eosinophilic cytoplasm and variable numbers of multinucleated giant cells, lymphocytes, and plasma cells (Fig. 10.10). The foam cells are distended with lipid, hemosiderin, or ceroid resulting from erythrocyte breakdown following nonphysiologic hemorrhage. PAS stains are positive at times. Cholesterol crystals, calcification, and necrotic debris typically are present.

Miscellaneous Infections

Two rare forms of endometritis of probable bacterial origin that produce specific morphologic changes are *pneumopolycystic endometritis*[209] and *malakoplakia*.[216,285] The former is characterized by the presence of multiple thin-walled cysts and vesicles lined by flattened cells. Multinucleated giant cells occasionally are present. A similar condition can be seen in the vagina (see Chapter 4, Diseases of the Vagina). The disease in the vagina is thought to result from infection by *Haemophilus vaginalis* or *Trichomonas*, but the etiologic agent in the endometrium is unknown. Malakoplakia most often involves the urinary bladder; the genital tract is rarely affected.[41,43,131,177,216,281,285,288,300] Patients with malakoplakia involving the genital tract range widely in age and may present with vaginal bleeding. Grossly, the lesions appear as soft, yellow, gray-brown plaques and nodules. Microscopically, the lesions are composed of a monomorphic population of histiocytes containing eosinophilic or clear cytoplasm (Von Hansemann cells), which may mimic xanthogranulomatous endometritis or clear cell carcinoma. The diagnosis of malakoplakia is made by the identification of intracellular and extracellular calcified spherules (Michaelis–Gutman bodies). *Escherichia coli* has been isolated most frequently from these lesions, but *Klebsiella* and *Proteus* spp. have also been identified. Malakoplakia may be related to a defect in the phagocytic function of monocytes–macrophages that leads to persistence of bacteria, which calcify to form Michaelis–Gutman bodies. Management consists of antibiotic treatment and surgical excision, but lesions may recur.

Dysfunctional Uterine Bleeding

During the reproductive years, the endometrium proliferates, differentiates, and sheds in a cyclic, predictable fashion in response to physiologic fluctuations in estrogen and progesterone levels. In ovulatory cycles, the luteal phase is 14 days in length, whereas the follicular phase is variable and may range from 10 to 20 days, yielding a wide range of cycle lengths among normal, ovulating women. Early after menarche, cycles tend to be long and irregular. After 5–7 years, cycles shorten to assume a regular pattern that is maintained until the perimenopause. In the fifth decade, cycles gradually lengthen, ceasing in the perimenopausal years. Data from a twin study suggest that genetics are a major determinant of both age at menarche and age at menopause, although these ages seem unrelated and probably are controlled by different genes.[255] Cycle length is based on the rate of follicular growth and maturation, which in turn is influenced by follicle-stimulating hormone (FSH) and inhibin secretion.[151] Abnormalities along the hypothalamic–pituitary–ovarian axis may result in a derangement of follicular maturation, ovulation, or corpus luteum

development, with subsequent abnormal hormone secretion. These alterations in the normal hormonal patterns may cause abnormal uterine bleeding, infertility, or both.

Dysfunctional uterine bleeding (*DUB*) is a clinical term used to describe bleeding not attributable to an underlying organic pathologic condition.[4,5,16,119,128,195,215,242,256] DUB is a diagnosis of exclusion rendered only after known causes of abnormal bleeding such as endometrial polyps, adenomyosis, leiomyomas, endometritis, atrophy, intrauterine devices, oral contraceptive use, abortion, ectopic pregnancy, hyperplasia, malignant tumors, gestational trophoblastic disease, blood dyscrasias, certain drugs (particularly anticoagulants), severe renal or liver disease, and hypothyroidism and hyperthyroidism have been ruled out.[166] Therefore, DUB is generally ascribed to poorly understood derangements in the functional effects of hormones on the endometrium.[262,263] Some, however, have also loosely applied this term to heavy, prolonged bleeding at the time of menses (i.e., menorrhagia). Bleeding resulting from anovulatory cycles is probably the most common cause of DUB in women of reproductive age. Also, either early decline or persistence of the corpus luteum may result in abnormal progesterone stimulation of the endometrium, causing DUB. Bleeding from breakdown of normal-appearing atrophic endometrium is the most common cause of postmenopausal uterine bleeding and is often discussed with DUB, although purists might consider this condition an explained source of bleeding. Finally, menorrhagia (if considered a form of DUB) is generally ascribed to local coagulation abnormalities associated with enhanced fibrinolysis and prostaglandin-mediated inhibition of platelet aggregation rather than the hormonally mediated mechanisms postulated in DUB.

Glandular and Stromal Breakdown Associated with Anovulation

In anovulatory cycles, one or more follicles develop in the ovary without the development of a corpus luteum. In these cycles, estradiol synthesized by follicular granulosa and theca cells stimulates endometrial proliferation, but stromal and glandular differentiation typical of the secretory phase fails to develop because progesterone is lacking. The follicles may persist and continue to produce estradiol, or they may regress, ending estrogen production. When estrogen levels decline, the endometrium can no longer be maintained, and bleeding ensues. The level of estrogenic stimulation is roughly linked to the pattern of bleeding. Relatively minimal estrogenic stimulation results in intermittent spotting that may be prolonged. Sustained endometrial stimulation by high levels of estrogen leads to prolonged amenorrhea followed by precipitous onset of heavy bleeding. Both these patterns have been referred to as estrogen breakthrough bleeding.[262,263]

Clinical Features

DUB related to anovulatory cycles typically occurs at menarche and at menopause but can occur at any time during the reproductive years.[195,284] In the first year after menarche, nearly 60% of cycles are anovulatory. Ovulatory cycles soon develop in most women, but some never establish normal cycles.[260] Women in this latter group may have infrequent, irregular periods or heavy bleeding, re-

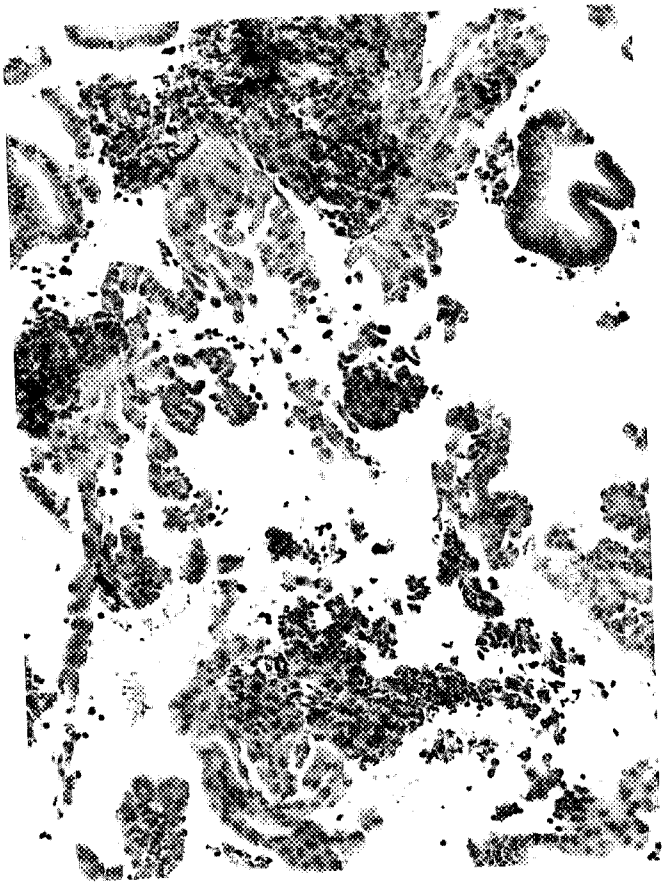

Fig. 10.11. Endometrial glandular and stromal breakdown. There is extensive fragmentation of endometrial glands. Strips of surface epithelium showing eosinophilic syncytial change are present in the *upper part* of the field. The stromal cells are condensed into tight clusters. These findings are typically found in association with anovulatory cycles.

quiring hospitalization. Some of these women display stigmata of polycystic ovarian disease, including obesity, infertility, and hirsutism (Stein–Leventhal syndrome) (see Chapter 16, Nonneoplastic Lesions of the Ovary). Many women in the reproductive age group with anovulatory cycles, however, do not manifest these classic clinical features. Although patients with polycystic ovarian disease are often anovulatory, up to 25% of cycles in these women may result in ovulation and formation of a corpus luteum.

Pathologic Findings

Histologic examination of endometrial tissue removed at the time of bleeding may be scant or abundant, depending on the duration and amount of bleeding that preceded the curettage. The glands are proliferative, but the degree of proliferation depends mainly on the duration of exposure to unopposed estrogen. Metaplasia, hyperplasia, and carcinoma may develop over a period of months or years (see Chapter 11, Precursor Lesions of Endometrial Carcinomas and Chapter 12, Endometrial Carcinoma). If estrogenic stimulation has been limited, the endometrium may appear extensively fragmented (Fig. 10.11), which can compromise the evaluation of glandular architecture, prompting both overdiagnosis and underdiagnosis of hyperplasia. In these cases, the glands should be carefully examined for features such as abnormal shape, cellular stratification, and nuclear atypia that may reflect concurrent breakdown and hyperplasia. Small fragments containing intact glands and stroma resembling typical proliferative endometrium may be seen (Fig. 10.12). As the ground substance undergoes dissolution, stromal cells condense and form compact nests of cells with hyperchromatic nuclei and little or no cytoplasm. The normal architecture collapses, and isolated, fragmented glands lie in haphazard disarray without surrounding stroma. Frequently, dark cytoplasmic granules may be identified in glandular cells, representing nuclear debris from necrotic cells. In combination, these features are referred to as glandular and stromal breakdown, and when present in a background of proliferative endometrium, suggest anovulatory bleeding. In cases with stronger estrogenic effects, the endometrium is less fragmented and more typical of normal proliferative endometrium with only focal areas of glandular and stromal breakdown (Fig. 10.13). If foci of dilated irregularly shaped glands with focal outpouchings and branching are present, the en-

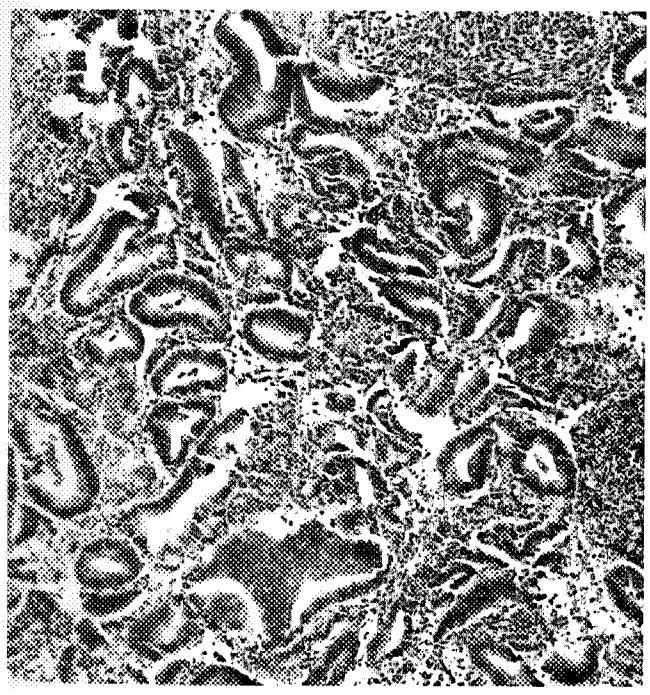

Fig. 10.12. Endometrial glandular and stromal breakdown. There is extensive fragmentation of proliferative glands, stromal necrosis, and hemorrhage.

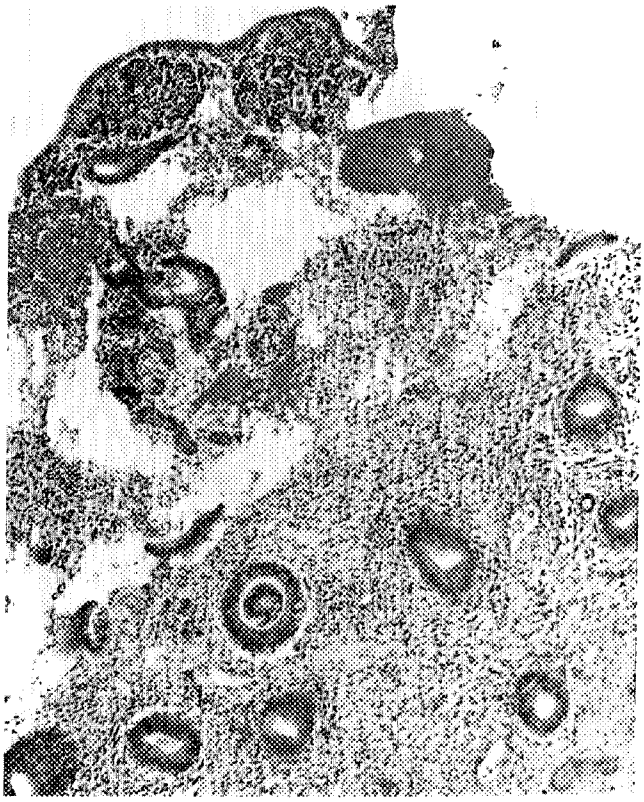

Fig. 10.13. Proliferative endometrium with focal breakdown. Most of the endometrium is in the proliferative phase. A focal area of breakdown is present on the surface in the *upper part* of the field.

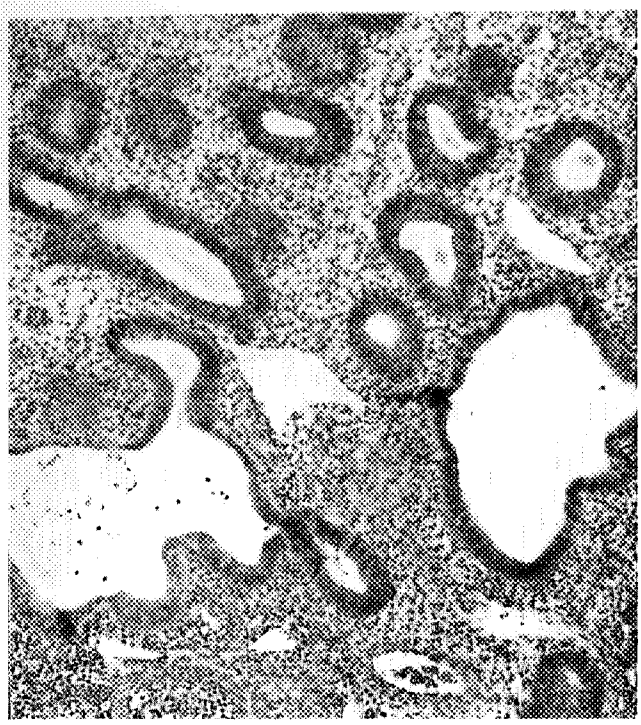

Fig. 10.14. Disordered proliferative phase. A few glands are enlarged and irregularly shaped.

dometrium is classified as disordered proliferative phase (Figs. 10.14 and 10.15).[103] Qualitatively, disordered proliferative phase resembles simple hyperplasia but the process is focal rather than diffuse (see Chapter 11, Precursor Lesions of Endometrial Carcinomas). Rare crowded glands with complex invaginations (Fig. 10.16) in an otherwise normal endometrium may represent an artifact that should not be confused with disordered proliferative phase or "focal" hyperplasia.

Papillary syncytial metaplasia is an epithelial alteration that is associated with stromal breakdown and bleeding. Because this lesion probably reflects a degenerative–regenerative process rather than a metaplastic one and formation of true papillae are lacking, alternative terms such as eosinophilic syncytial change, papillary syncytial change, or surface syncytial change have been proposed[317] (see Chapter 11, Precursor Lesions of Endometrial Carcinomas). These lesions typically involve the surface but glands may also be involved. Typically, cells with eosinophilic cytoplasm, indistinct cell membranes, and moderately prominent nucleoli form microscopic mounds on the endometrial surface overlying condensed stromal cells (Figs. 10.11 and 10.17).

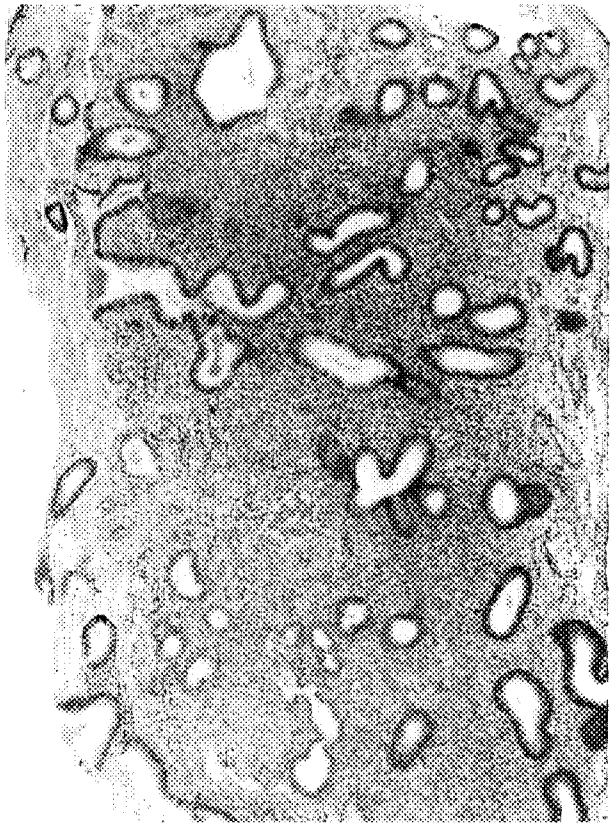

Fig. 10.15. Disordered proliferative phase. Most of the endometrium is in the proliferative phase but a few scattered glands that are enlarged and irregularly shaped are present.

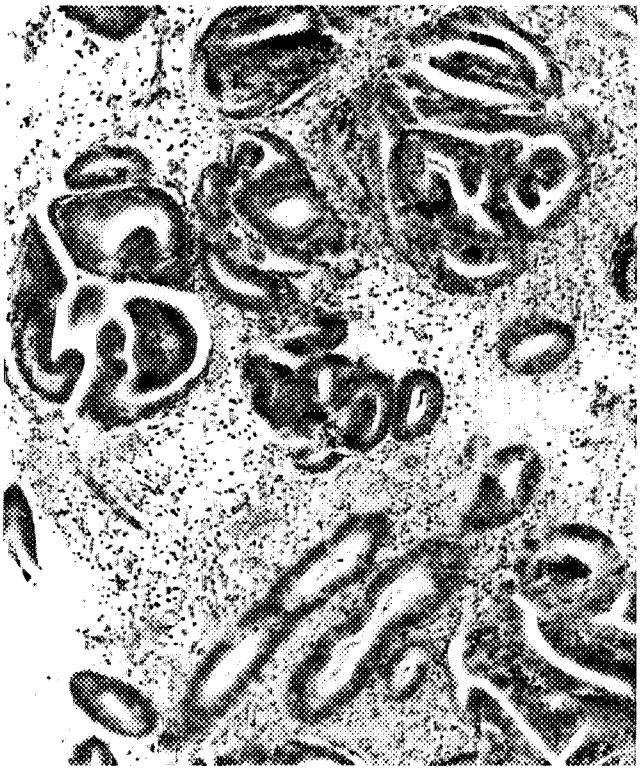

Fig. 10.16. Focal glandular crowding. The endometrium is in the proliferative phase. The crowding and the convoluted appearance of the glands are artifactual changes.

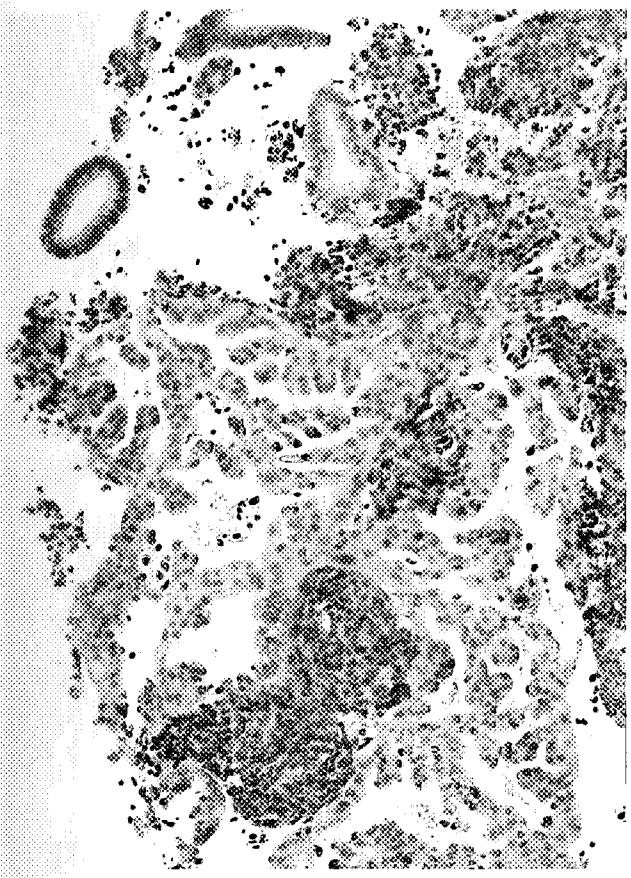

Fig. 10.17. Eosinophilic syncytial change. Cells with eosinophilic cytoplasm form a syncytium that envelops clusters of stromal cells.

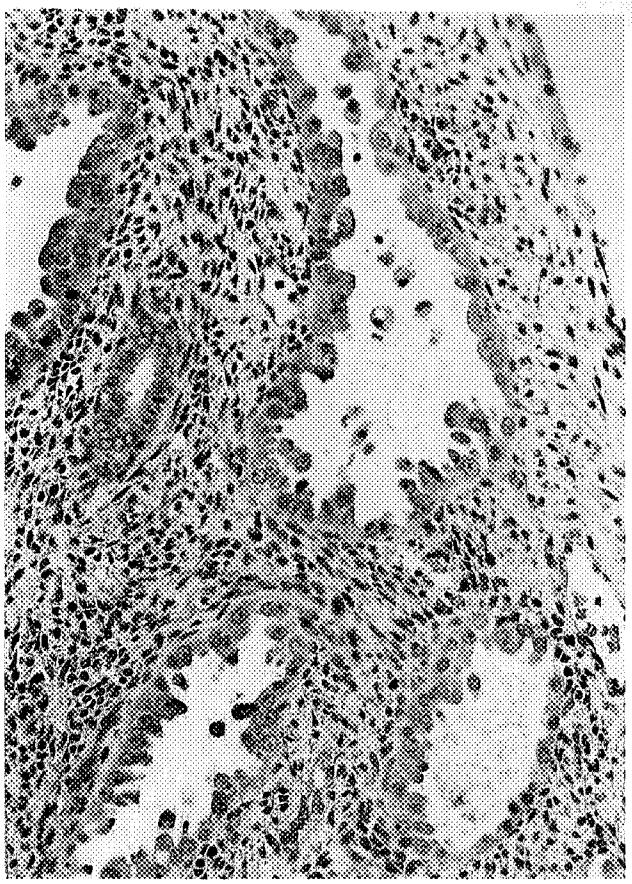

Fig. 10.18. Eosinophilic and hobnail cell change. Cells have enlarged, rounded nuclei, some of which contain small nucleoli. This change should not be interpreted as "atypia." Some cells protrude into the lumen (hobnail change).

Microcysts containing PMNs and nuclear debris may be present within the cell masses.

Another common finding associated with bleeding and breakdown is termed *eosinophilic change* or *eosinophilic metaplasia*. This change is characterized by cells with abundant eosinophilic cytoplasm, nucleolar prominence, or mitoses reflecting epithelial regeneration or smudgy, hyperchromatic chromatin reflecting degeneration (Fig. 10.18). Eosinophilic change, also referred to as eosinophilic syncytial change when the cell borders of the cells are not evident, may mimic the significant atypia found in endometrial intraepithelial carcinoma or atypical endometrial hyperplasia. However, the changes in papillary syncytial metaplasia are usually more delimited than in precursor lesions and the degree of nuclear enlargement, pleomorphism, and irregularity is comparatively modest. Eosinophilic syncytial change may be associated with other cytoplasmic alterations (metaplasias) including squamous, mucinous, and ciliated change (see Chapter 11).

In abnormal shedding, the endometrium often displays thin-walled ectatic venules that may contain prominent fibrin thrombi (Fig. 10.19), a feature seldom encountered in normal menstrual endometrium. Bleeding during a normal menstrual cycle is a consequence of rhythmic vasospasm and relaxation of the spiral arterioles, resulting in a complete, yet self-limited sloughing of the functionalis (see Chapter 9, Anatomy and Histology of the Uterine Corpus).[224] In anovulatory cycles, spiral arterioles fail to develop adequately, and the dilated, thin-walled venules undergo thrombosis. Stromal necrosis involving random portions of the endometrium results in incomplete shedding. Consequently, the bleeding pattern is asynchronous and highly variable in duration.

Differential Diagnosis

Artifactual glandular crowding secondary to stromal collapse may superficially resemble hyperplasia or carcinoma (Fig. 10.20). However, the glands in glandular and stromal breakdown typically have normal shapes and the epithelium lacks stratifica-

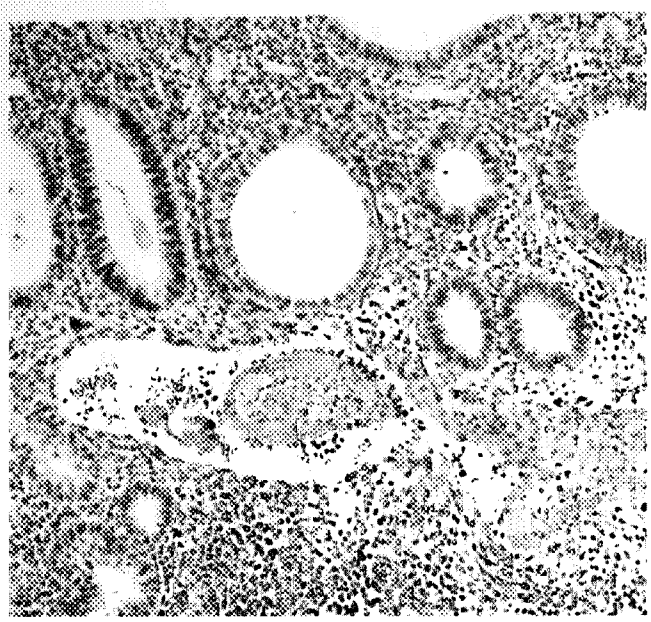

Fig. 10.19. Fibrin thrombi in association with glandular and stromal breakdown. Dysfunctional bleeding associated with anovulatory cycles may result in mild irregularities in proliferative glands and in the development of thin-walled blood vessels. Bleeding is caused, in part, by disruption of the capillaries that contain fibrin thrombi.

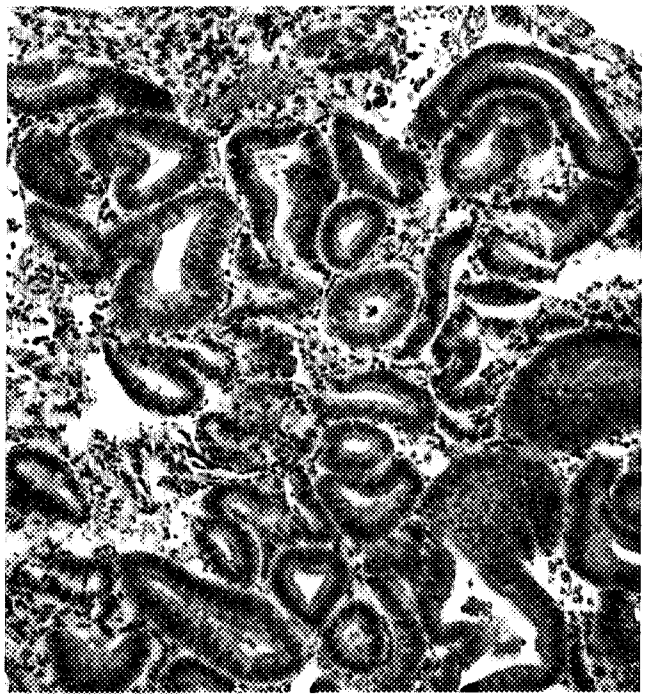

Fig. 10.20. Pseudoglandular crowding in glandular and stromal breakdown. The glandular crowding results from breakdown and dissolution of the intervening stroma; this should not be confused with crowding as a result of hyperplasia.

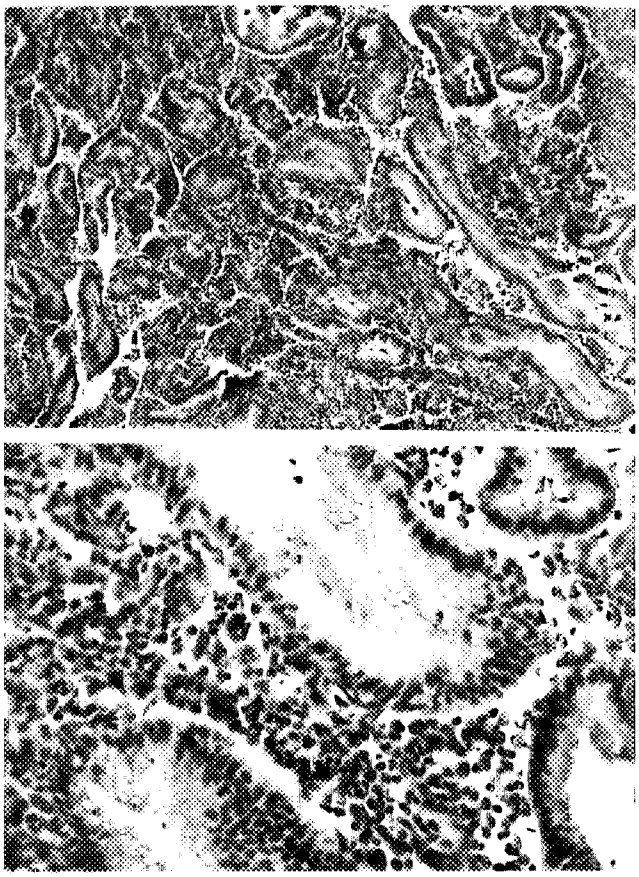

Fig. 10.21. Menstrual endometrium. *Top*: Diffuse hemorrhage, necrosis, and stromal breakdown. *Bottom*: Numerous glands containing vacuolated cytoplasm.

tion, atypia, and significant mitotic activity. In menstrual endometrium, a predecidual reaction is present and the glands are typically dilated and filled with secretions (Fig. 10.21). Degenerative cytoplasmic vacuolization may be seen in either.

Treatment

Treatment depends on the age of the patient. An acute bleeding episode in a woman under 35 years of age may respond to a short course of low-dose combination monophasic birth control pills.[262,263] The progestin stabilizes the uterine vasculature, differentiates the glands and stroma, and results in a complete shedding of the endometrium when therapy is discontinued. Bleeding may be heavy, but it is self-limited. In women over 35 years old and in young women with bleeding not controlled by hormones, an endometrial biopsy to rule out organic pathology should be considered. In young women with recurrent anovulatory cycles who are not immediately desirous of childbearing, a week's course of oral medroxyprogesterone acetate (Provera) every

2 months will prevent excessive endometrial buildup and should give controlled withdrawal bleeding. If bleeding occurs in an anovulatory patient who is infertile, successful induction of ovulation with clomiphene may achieve normal ovulatory cycles and menstrual shedding. Bleeding that cannot be controlled by medical treatment requires surgical intervention. Options include hysterectomy and endometrial ablation using a laser or resectoscope with a loop or rolling ball electrode.[160]

Atrophy

Bleeding associated with *endometrial atrophy* related to insufficient estrogen stimulation may develop in women taking oral contraceptives, in postmenopausal women with naturally occurring atrophy, in young women with premature ovarian failure, or following radiation for cervical cancer. Typically, patients complain of vaginal spotting. Atrophy may account for up to 82% of postmenopausal vaginal spotting or bleeding.[44,87,153,172,229,240] The microscopic appearance of atrophic endometrium is different in hysterectomy and biopsy specimens.[166,316] In hysterectomy specimens, the endometrium is thin and composed of variably sized glands that are often cystic and surrounded by a diminished amount of compact stroma compared with endometria from reproductive age women. The glands are lined by a single layer of flattened or cuboidal cells containing bland nuclei without mitoses. Under low magnification, cystically dilated atrophic glands may mimic simple hyperplasia, but the epithelial cells are not stratified, mitotic figures are absent, and the cells possess little cytoplasm. Biopsy or curettage specimens of atrophic endometrium typically consist of scant mucus with rare fragments and strips of cuboidal or columnar cells. Intact glands may be absent (Fig. 10.22), and only small clusters of stromal cells with dark ovoid nuclei resembling those seen in anovulatory bleeding are observed. Cases containing scant epithelium may be considered adequate provided that the cells can be definitively recognized as atrophic endometrium and not endocervical. These specimens should not be diagnosed as being insufficient for diagnosis because this amount of tissue generally is all that is present, even after a thorough curettage. Such specimens should be given a descriptive diagnosis, for example, "scant fragments of atrophic endometrial tissue."

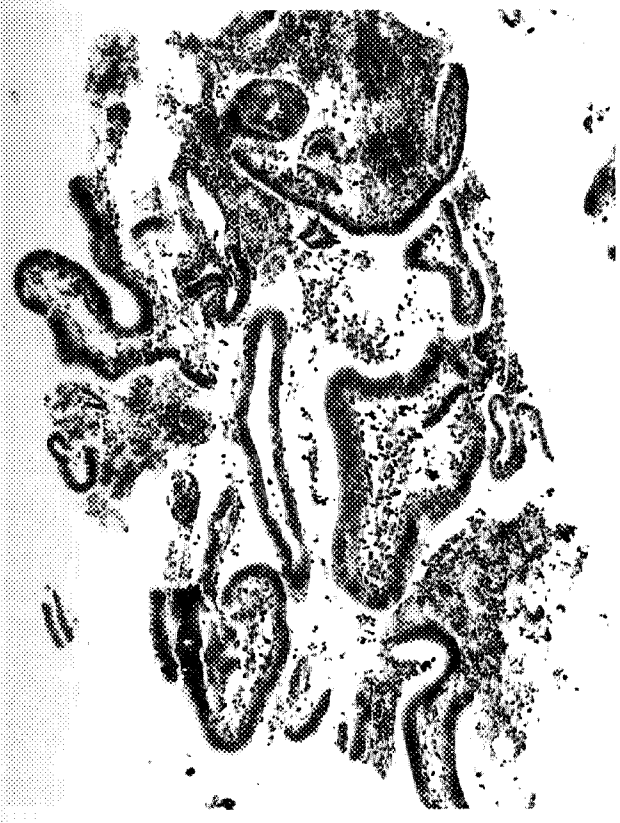

Fig. 10.22. Atrophy. Atrophic endometrium in curettings is characterized by strips of surface endometrium, fragmented glands, and minimal stroma.

Inadequate Luteal Phase

Inadequate luteal phase, or *luteal-phase defect* (*LPD*), is thought to result from inadequate progesterone secretion by the corpus luteum and is usually diagnosed during an evaluation for infertility or abnormal bleeding. The pathogenesis of LPD is complex and poorly understood. In many cases, LPD develops when the corpus luteum either fails to develop adequately or regresses prematurely. It is postulated that a poorly formed corpus luteum may be caused by inappropriately low FSH levels during the follicular phase or low FSH and luteinizing hormone (LH) peaks at midcycle, leading to deficient luteinization of the granulosa cells.[262,263] Elevated prolactin levels may also lead to LPD by suppressing progesterone release by the granulosa cells. Any of these processes could reduce total progesterone secretion by the corpus luteum. Studies suggest that LPD may reflect an end-organ receptor defect, in view of the finding of a reduced number of endometrial progesterone receptor-binding sites in some patients with LPD.[145,264] As a result, menses occurs 6–9 days after the LH surge.[124,125,180]

Clinical Features

In most studies, LPD is found in only 3–5% of infertile women,[295] and its significance remains controversial because controlled studies are lacking. LPD may also contribute to early habitual spontaneous abortions and to abnormal uterine bleeding.[113] The diagnosis of LPD requires the demonstration of the diagnostic findings in at least two consecutive cycles because similar changes occur sporadically in normal women.[126] Endometrial biopsy is considered one of the best methods of establishing the diagnosis,[8,61,294] but basal body temperature graphs showing a temperature rise that is sustained for less than 10 days and low serum progesterone levels are valuable adjuncts.[57,61,226,262]

Pathologic Findings

Exact pathologic criteria for the diagnosis of LPD have not been definitively established. Characteristically, the endometrium resembles normal secretory endometrium but shows an appearance that is consistent with a date that is at least 2 days earlier than expected (in two consecutive cycles), according to the basal body temperature graph and the onset of menses after biopsy (e.g., a day 24 pattern on day 26).[180,259] In normally cycling women, endometrial dating is, at best, an approximation, with variation from one microscopic field to another and between observers. Reproducibility of endometrial dating is within 2 days of the expected date in about 80% of cases.[196] The secretory pattern in LPD varies with the patient's hormone balance, and dating is often impossible due to a discordant appearance of the glands and stroma.[60] For example, glands may show secretory changes but lack the complex tortuosity expected, or the stroma may fail to show edema or predecidual changes in an endometrium that otherwise resembles late-secretory phase. The pathologic changes in benign secretory endometrium attributable to hormonal imbalances have not been well characterized. Consequently, abnormal-appearing secretory-phase endometrium may reflect LPD, but the changes are not diagnostic.

Treatment

Various treatments have been used for LPD. If low FSH and LH levels are implicated, clomiphene citrate or human menopausal gonadotropin is used to cause an elevation of FSH.[71,262] Progesterone vaginal suppositories administered after the midcycle temperature rise have also been tried in an attempt to alleviate a presumptive deficiency of progesterone in LPD.[125,259,296] Alternatively, human chorionic gonadotropin (hCG) may be administered to patients with hyperprolactinemia to stimulate the corpus luteum to produce progesterone,[262] or bromocriptine, to inhibit prolactin secretion.[65]

Irregular Shedding

Irregular shedding is diagnosed when endometrial tissue obtained at least 5 days after the onset of bleeding shows a mixture of secretory and proliferative patterns (Fig. 10.23). It is a rare cause of abnormal bleeding in women between 24 and 50 years of age.[168,284] It is characterized by prolonged, heavy bleeding at the time of menses, sometimes lasting longer than 2 weeks.[169,254] Irregular shedding may occur at every menstrual period or only once, such as with a persistent corpus luteum cyst. The mechanism underlying irregular shedding with a persistent corpus luteum is presumably prolonged exposure to progesterone because injecting small doses

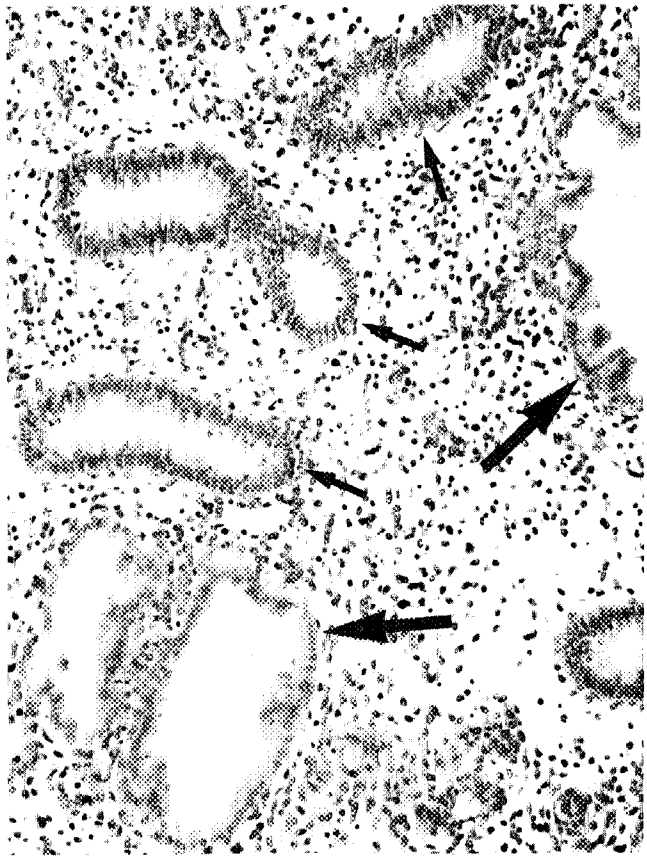

Fig. 10.23. Irregular shedding. Glands showing secretory exhaustion (*large arrows*) are immediately adjacent to proliferative glands (*small arrows*) in an edematous, secretory-type stroma.

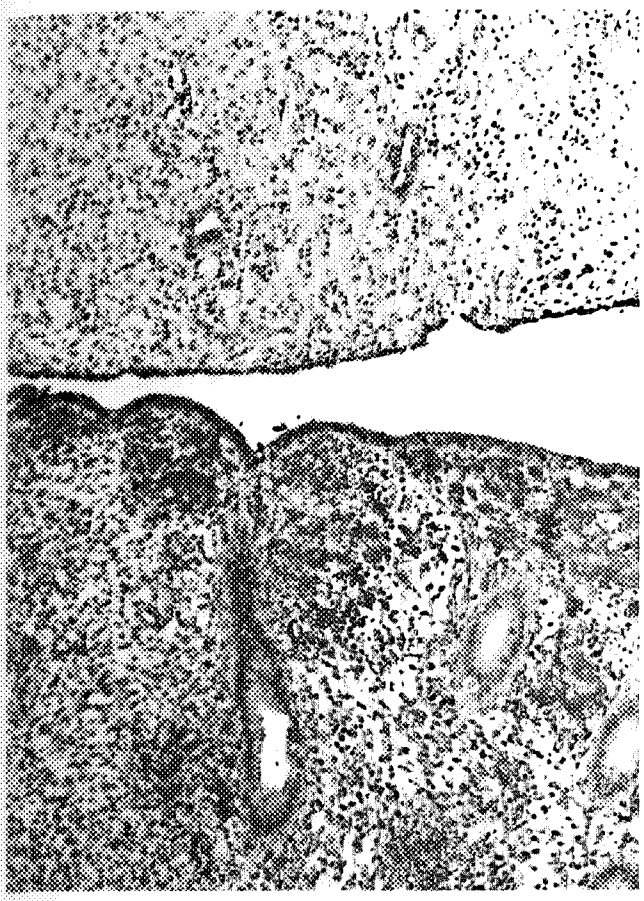

Fig. 10.24. Irregular shedding. *Top*: A secretory pattern with a predecidual reaction. *Bottom*: A proliferative pattern.

of progesterone during the menstrual phase of the cycle produces similar effects.[111] Microscopically, a diverse array of endometrial fragments containing irregular star-shaped secretory glands admixed with early proliferative glands are seen.[60] The stroma around proliferative glands is dense and compact. In areas containing secretory-type glands, the stroma is edematous and the stromal cells may be converted into predecidual cells (Fig. 10.24). Fibrin thrombi may be present. In addition, there is frequent evidence of glandular and stromal breakdown. In contrast to LPD, which shows only secretory changes, irregular shedding demonstrates secretory and proliferative changes. Other endometrial disorders, including abortions, polyps, and chronic endometritis, may produce bleeding patterns that mimic irregular shedding. In addition, there are abnormal secretory patterns with superimposed bleeding for which there are no specific clinical correlations. Accordingly, these abnormal secretory patterns are best given a descriptive diagnosis.

Unexplained Menorrhagia

In contrast to DUB related to hormonal imbalances, some unexplained menorrhagia may be related to abnormal mechanisms of local hemostasis.[114,287] Ultrastructurally, clots in women with menorrhagia appear different than those in normal women, and abnormal platelet aggregation related to alterations in prostaglandin synthesis have been suggested.[3,35] Enhanced fibrinolysis has also been proposed as a mechanism in these women.[93,232] Studies have found that women with essential menorrhagia have higher levels of tissue plasminogen activator activity in the menstrual phase and higher levels of the corresponding antigen in both the late-secretory and menstrual phases than controls. Accordingly, treatment with prostaglandin synthetase inhibitors may be highly effective in reducing bleeding in these women. Use of progesterone-releasing intrauterine devices may also be effective.

Effects of Drugs

Estrogens

The endometrium is sensitive to low concentrations of *estrogen*, with most pathologic effects more strongly related to duration of exposure rather than the dose. In rabbits, prolonged estrogen exposure induces endometrial carcinoma,[171] whereas high doses in monkeys result in atrophy.[102] In humans, prolonged administration of estrogens may produce hyperplasia and endometrioid adenocarcinoma (see Chapter 11, Precursor Lesions of Endometrial Carcinomas, and Chapter 12, Endometrial Carcinoma).[199] Estrogen may also result in proliferative-phase patterns and in glandular and stromal breakdown resembling the findings in DUB caused by anovulatory cycles. In addition to inducing proliferation, estrogens, probably in combination with other hormones, may promote epithelial differentiation, including formation of cilia (tubal metaplasia) and cytoplasmic eosinophilia[103] (see Chapter 11).

Tamoxifen

Tamoxifen acts as a partial estrogen receptor agonist and antagonist. In the endometrium, the former properties dominate, whereas the antiestrogenic properties are responsible for the effectiveness of tamoxifen as a breast cancer treatment and its possible use in chemoprevention. Results from the National Surgical Adjuvant Breast and Bowel Pro-

ject Breast Cancer Prevention Trial (P-1) demonstrated that 5 years of tamoxifen use at a dose of 20 mg/day reduced breast cancer risk in high-risk women by 49%. It is unclear how much of this benefit reflected true chemoprevention or simply suppression of cancers already present at study enrollment. Tamoxifen recipients had a risk ratio of 2.5 for the development of endometrial carcinoma. All the tumors were stage I, and there were no reported deaths related to these tumors.[77]

In a case-control study of 309 women diagnosed with malignant endometrial tumors after a diagnosis of breast carcinoma and 860 matched breast cancer controls, Bergman et al. found that tamoxifen use was associated with a relative risk of 1.5 for the development of endometrial cancer.[19] Risk was strongly associated with duration of use, with a relative risk of 6.9 for women receiving 5 years or more of treatment. Treatment for 2 years or more was associated with a higher frequency of advanced stage tumors, sarcomas, malignant mixed müllerian tumors, and shortened survival. Cancer risk was associated with cumulative dose but not with daily dose. Kedar et al. reported, in a randomized trial of 111 healthy women with family histories of breast cancer given tamoxifen or placebo, that patients receiving tamoxifen had thicker endometria and significantly more often developed endometrial pathology. Most notably, endometrial hyperplasia was identified in 16% of the treated group compared to none of the controls.[132] Fornander et al. also reported that tamoxifen users have a relative risk of 6.4 at 3–4 years for developing endometrial carcinoma compared to nonusers[80] (see Chapter 12, Endometrial Carcinoma). These results are concordant with the bulk of evidence suggesting that tamoxifen use is causally related to the development of endometrial proliferation, hyperplasia, and carcinoma.[118]

Although some studies suggest that tamoxifen-associated carcinomas tend to be more aggressive and skewed toward high-risk types,[161,250] there is at least equal evidence that these carcinomas are similar in grade, stage, type, and behavior to cancers arising in nonusers.[14,118] However, studies have been small and some may not have accounted fully for all prognostic variables. Some studies suggesting an overrepresentation of aggressive tumor types compared to the general population have included patients receiving 40 mg/day instead of 20 mg/day of famoxifen (usual dose for adjuvant treatment of breast cancer in the United States) or may have reflected a referral bias because the research was conducted at tertiary centers.[161,250]

Other uterine abnormalities that have been associated with tamoxifen use include endometrial polyps, hyperplasia, sarcomas, adenomyosis, endometriosis, and leiomyomas.[66,86,188] The appearance of endometrial polyps in tamoxifen-treated patients is generally similar to those occurring spontaneously.[51] Stromal decidualization may reflect concurrent administration of progesterone. Tamoxifen-associated endometrial polyps tend to be large and multiple. These polyps often have a myxoid or edematous stroma and staghorn gland that may be polarized along the long axis of the polyp. Metaplasias and carcinomas may occur in these polyps.[49a,133a]

Tamoxifen has also consistently been associated with an increased incidence of endometrial polyps,[49,147] but potentially important confounding factors such as baseline endometrial status and body fat distribution were not taken into account.[188] Raloxifen is a benzo-thiophene-selective estrogen-receptor modulator that may also reduce breast cancer risk, but in contrast to tamoxifen, raloxifen does not seem to increase endometrial thickness, produce bleeding, or induce endometrial proliferation or hyperplasia.[48,96] The STAR trial (study of tamoxifen and raloxifen) should shed light on the potential value of these agents in chemoprevention.

Estrogen and Progesterone Therapy in Postmenopausal Women

Hormone replacement therapy has been administered to many postmenopausal women to alleviate menopausal symptoms, including abnormal bleeding, and to reduce the risk of osteoporotic fractures and death from coronary artery disease.[62,74] Use of hormone replacement had increased dramatically in the United States. During the period 1982–1992, progesterone prescriptions increased 2.3 fold and those for progesterone 4.9 fold.[309] Data from the Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial have demonstrated that estrogen or estrogen/progestin combination therapy has salutary effects on lipoprotein levels.[282] However, it is unclear whether improvement in lipid profiles translates into reduced cardiovascular mortality. In the PEPI Trial, estrogen alone demonstrated the highest elevation in the cardioprotective high-density lipoprotein cholesterol, but 34% of recipients developed adenomatous (complex) or atypical hyperplasia, making this regimen suitable only for women without a uterus.[283] Medical intervention was successful in reversing these lesions in all but 2 of 10 women with atypical hyperplasia. The reported occurrence of endometrial hyperplasia in women taking estrogen alone is similar to that reported in other studies.[47] The risk of endometrial carcinoma is also greater in women on unopposed estrogen as compared with untreated women.[289] After 1 year of

treatment, risk of endometrial carcinoma may remain increased for more than 10 years after discontinuation of therapy. Accordingly, a progestational agent given either continuously with estrogen or sequentially for 10–14 days in the latter half of the cycle is usually included in hormonal replacement therapies. By adding a synthetic progestational agent or natural progesterone, the rate of hyperplasia is reduced substantially when the dose and duration of treatment are optimized.[47,269,299]

Effects of progesterone depend on type, dose, and duration of use, as reviewed by Song and Fraser.[257] Salient effects include inhibition of glandular proliferation, stromal decidualization, stromal necrosis, and recruitment of leukocytes. Based on screening results of 2964 peri- and postmenopausal candidates for hormone replacement therapy showing only 0.6% with hyperplasia and 0.07% with adenocarcinoma, Korhoneen et al. suggested that biopsy before initiating hormone replacement therapy is not required in asymptomatic women.[138] The average age of women in this study was 52 years, with a last menstrual period 29 months before enrollment. Sequential regimens originally were used in doses that were high enough to induce secretory transformation and result in cyclic withdrawal bleeding. Many postmenopausal women, however, find regular bleeding objectionable and consequently compliance is poor with this regimen. A continuous regimen employing reduced doses of estrogen and progesterone that results in an atrophic endometrium and amenorrhea has also been used. Cases of hyperplasia or carcinomas were not identified in a study of 236 women treated for more than 5 years with this combined therapy, and mitotic activity was low.[185] The amount of tissue obtained via endometrial biopsy in this study was associated with the dose of estrogen and progesterone used and the bleeding pattern. Recovery of endometrial tissue was 100% with high doses but only 18% with low doses. Tissue was not obtained in 83% of amenorrheic patients but was collected in 93% of women with regular withdrawal bleeding. Hysteroscopic examination confirmed the presence of endometrial atrophy in women with scant specimens. This study demonstrated that low doses of progesterone inhibit endometrial proliferation, resulting in endometrial atrophy and amenorrhea without inducing secretory maturation. Protection from hyperplasia equaled the higher-dose regimens, which resulted in regular bleeding (Moyer, personal communication).[185]

Williams et al. investigated the effects of giving 0.625 mg/day estradiol with 10 mg/day medroxyprogesterone acetate in three different regimens: 14 days of progestational treatment every 28 days, 14 days every 84 days, or 28 days every 84 days.[302] Women receiving the least amount of progesterone in the 84-day period had the least bleeding. Simple hyperplasia was recognized in 1% of each group. Nand et al. reported that among 568 postmenopausal women receiving 1.25 mg/day estrone sulfate and either 2.5, 5.0, or 10.0 mg/day medroxyprogesterone acetate, 80% became amenorrheic at 6 months and none developed hyperplasia.[187] Similarly, in a randomized, double-masked multicenter trial of 1176 postmenopausal women, 14.6% of patients receiving 1 mg/day estradiol developed hyperplasia within 1 year compared to less than 1% of those given combination treatment with norethindrone acetate at doses as low as 0.1 mg daily.[143] Although both the sequential and combined hormone replacement regimens and oral contraceptives contain estrogen and progesterone, hormone replacement regimens contain much lower doses and produce different histologic effects.

The histologic appearance of the endometrium in women receiving hormone replacement varies depending on the dosage, duration of use, regimen (combined or sequential), status of the endometrium before therapy, and the time in the cycle when the biopsy is obtained. Possible appearances include normal-appearing proliferative or secretory endometrium, mixed proliferative and secretory endometrium, abnormal secretory patterns, and atrophy. Secretory endometria can show variable secretory activity with or without predecidual change (Figs. 10.25 and 10.26). In addition, disordered proliferative phase, hyperplasia, and various types of cytoplasmic changes (metaplasias) can be observed.[64] Low-dose preparations produce endometrial atrophy or secretory changes that are not as fully developed as those in the normal luteal phase.[166] In postmenopausal women, decidualization usually reflects the use of a relatively high-dose hormone replacement regimen; idiopathic decidual reactions in postmenopausal women have been reported rarely.[45] Arias–Stella reaction has also been reported in nonpregnant patients, especially in the setting of exogenous hormone administration including progestational agents.[116]

Contraceptive Steroids (Progestin-Estrogen Agents)

The chemical composition, metabolism, and effects of *contraceptive steroids* differ from those of naturally occurring hormones. Naturally occurring estrogens are inactivated when administered orally, but oral contraceptives contain an orally active agent, 17-alpha-ethinylestradiol, produced by adding

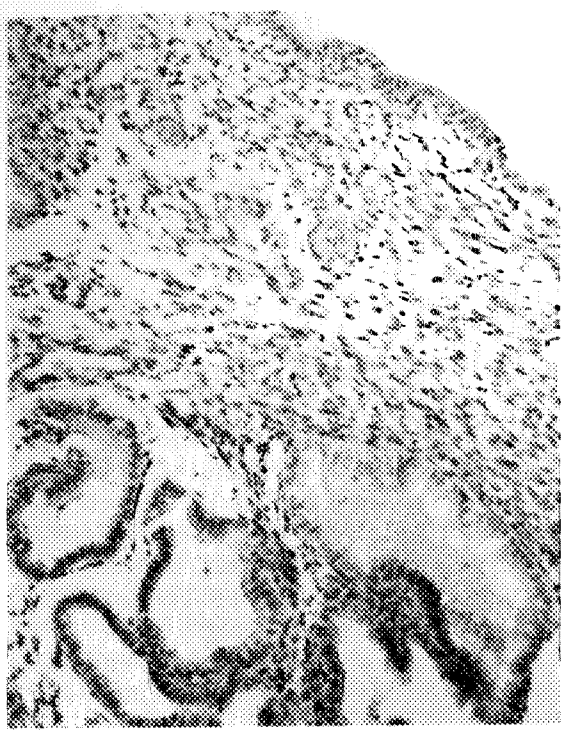

Fig. 10.25. Estrogen and progesterone hormone replacement therapy. The glands are variable in appearance. One gland contains secretory material in the lumen and the others are lined by nondescript epithelium, which represent a weak secretory response. The stroma is composed of spindle-shaped cells. There is no evidence of a predecidual reaction. (Courtesy of Dr. Dean Moyer, Los Angeles, CA.)

Fig. 10.26. Estrogen and progesterone hormone replacement therapy. The endometrium shows full secretory maturation. Glands show secretory exhaustion, and the stroma has undergone a predecidual change. (Courtesy of Dr. Dean Moyer, Los Angeles, CA.)

an ethinyl group to position 17. The less potent 3-methyl ether derivative of ethinylestradiol, mestranol, is also used as the estrogenic component of oral contraceptives. Some oral contraceptives have profound progestational activity, which may be 50 times more potent that natural progesterone. Also, some progestational agents are metabolized to estrogenic compounds in the body.[262] Potency of different progestins varies considerably, and biologic effects depend mainly on potency rather than on dosage. The progestational agents in the combination pill prevent ovulation by inhibiting LH secretion through a negative feedback effect on the hypothalamus. Although the estrogen component in the pill exerts a similar effect on FSH, its primary function is to stimulate endometrial proliferation, thereby preventing breakthrough bleeding. Estrogen also potentiates the negative feedback action of the progestational agent, permitting the use of a lower dose of the latter. This effect is attributed to estrogen increasing the intracellular concentration of progesterone receptors.[262,263]

Clinical Features

In the past, contraceptive steroids were administered either as a sequential regimen in which estrogen alone was taken for 14–16 days, followed by 5–6 days during which the estrogen and progestin were given in a single tablet, or as a combined regimen in which a synthetic estrogen was combined with a synthetic progestin in a single tablet taken on day 5 of the cycle and continued for 21 days. The sequential regimen was introduced with the expectation that it would be tolerated better because it more closely simulated a woman's natural endocrine milieu. However, sequential pills proved to be less reliable contraceptive agents, with breakthrough ovulations reported in about 8% of women.[170] These agents were withdrawn from the market in the United States and Canada in 1976 after reports linking them to endometrial cancer surfaced.[133,158,251,252] Notably, 83% of sequential pill users who developed endometrial carcinoma used Oracon.[158,251] and the elevation in risk was supported by an epidemiologic study.[292] This study also suggested that endometrial carcinoma risk is reduced in women taking combined oral contraceptives, as would be expected from the suppressive effect of progestin-dominated combined regimens. The carcinogenic effect of Oracon does not seem to have been attributable simply to the effects of unopposed estrogen because other sequential pills were not associated with the development of endometrial carcinoma. Oracon, however, used a high dose (100 μg) of the potent

estrogen ethinylestradiol combined with a weak progestin, which insufficiently opposed the estrogenic effect.

Continued use of oral contraceptives, particularly the low-dose preparations (20–35 μg ethinylestradiol), may result in breakthrough bleeding or amenorrhea.[176] Secondary amenorrhea may occur because the low estrogen content of the pill frequently is inadequate to stimulate endometrial growth. Consequently, there is insufficient tissue to produce withdrawal bleeding at the end of a pill cycle. A pill with a slightly higher estrogen content helps in this situation. Prolonged use of oral contraceptives results in the development of thin-walled vascular sinusoids located beneath the endometrial surface, which become ectatic and undergo thrombosis. The endometrial vessels become disrupted and bleed and the surrounding tissue shrinks but is not shed completely, which is manifested clinically as breakthrough bleeding. A 7-day course of conjugated estrogens or ethinylestradiol daily will build up the endometrium and result in uniform withdrawal bleeding.[262,263]

Pathologic Findings

The histologic alterations produced by oral contraceptives on the endometrium are a function of (1) whether the drugs are administered in the combined or sequential regimen, (2) the dose and duration of drug used, (3) the morphologic appearance of the endometrium before the start of therapy, and (4) the time of the cycle when the tissue is obtained for study.[105,166,197,198] During the first cycle of the combined regimen in women who had previously been ovulating normally, the proliferative phase is markedly shortened, with an arrest in both the growth and differentiation of the glandular epithelium. The glands remain straight and are lined by a single layer of low, inactive columnar epithelium. Glycogen vacuoles appear prematurely and tend to be randomly distributed (Fig. 10.27). Glandular growth is inhibited, and secretory changes develop minimally, if at all. Stromal edema, which can be striking early in therapy, gives way to a distinct decidual change, and numerous granular lymphocytes appear (Fig. 10.28). After long-term contraceptive use, there is no evidence of secretory activity. The endometrium undergoes atrophy and is composed of sparse, narrow glands.[42] The remaining glands are composed of flattened epithelial cells. In addition, thin-walled vascular sinusoids develop and the stroma is decreased. A decidual reaction may not be evident. This is the usual appearance of the endometrium in women using the low-dose formulations.

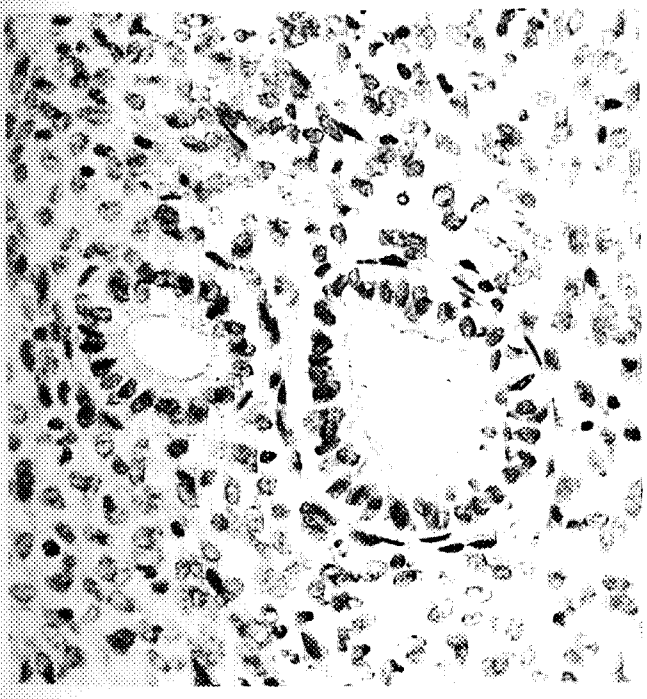

Fig. 10.27. Oral contraceptive therapy. Secretory vacuoles appear prematurely in endometrial glands early during the course of combined oral contraceptive administration.

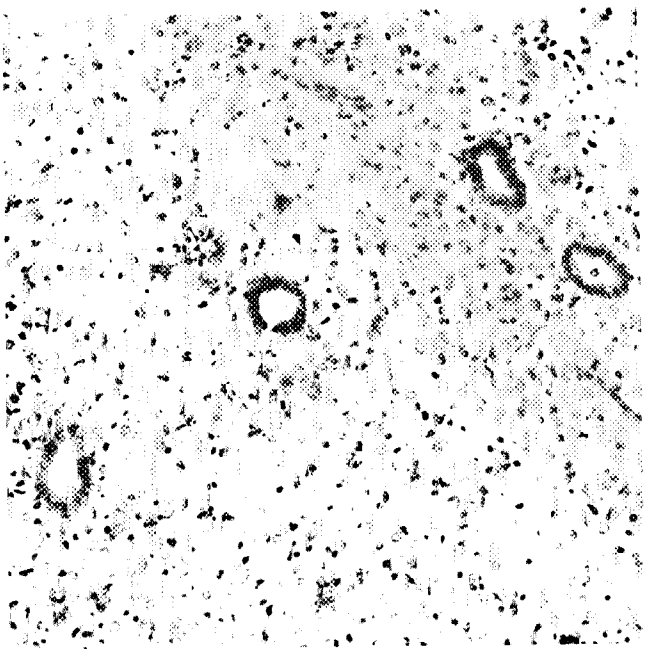

Fig. 10.28. Oral contraceptive therapy. After several cycles of oral contraceptives, the endometrium shows a marked decidual reaction. Glands are small and lined by inactive epithelium.

Progestins, Including Norplant

Progestin-type drugs alone produce effects on the endometrium similar to those described for combined oral contraceptives, but atrophy develops earlier. A marked decidual reaction and glandular suppression of the endometrium may be induced with intramuscular injection of medroxyprogesterone acetate (Depo-Provera). A similar effect is observed with intrauterine devices (IUDs) impregnated with progesterone, but the effect is confined to the superficial endometrium. High-dose progestin therapy has been used in the medical treatment of endometrial hyperplasia in young women who wish to retain their fertility or in older women who are poor surgical candidates. Glands with abnormal shapes and crowding typical of hyperplasia may persist but the glandular cells show secretory changes, including the presence of vacuoles. Mitotic activity is decreased, and the stroma becomes decidualized. Typically, the initial findings are patchy with only some foci showing suppression of the hyperplastic process. Accordingly, patients treated in this manner must undergo repeated curettages, both to remove hyperplastic tissue and to monitor treatment response.

An unusual type of stromal atypia, referred to as pseudomalignant[69] or pseudosarcoma,[56] has been reported in women receiving high-dose progestational oral contraceptives (Fig. 10.29). Although this lesion is rarely seen now because of the use of low-dose oral contraceptives, the change may be seen in women being treated with progestational agents for endometrial hyperplasia because of the high doses that are used. Norplant is a long-acting, reversible contraceptive method that is introduced under the skin and releases small amounts of levonorgesterol at a relatively constant rate for as long as 5 years. The pregnancy rate during the first 3 years of use is comparable to tubal sterilization.[248] As with other progestins, the mechanism of action may be multifactorial: suppression of ovulation, increase in the viscosity of cervical mucus, and suppression of endometrial growth. The main endometrial change is gland atrophy and stromal decidualization.[55] As with other progestin-only contraceptives, pregnancies that do occur are often ectopic (20–30%) because progestins inhibit tubal motility.

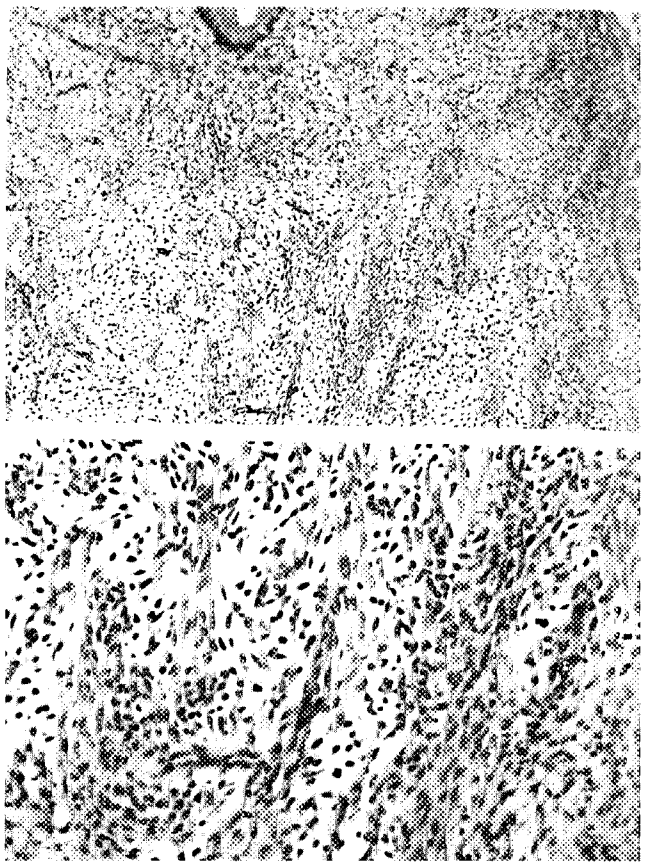

Fig. 10.29. High-dose progesterone effect showing a "pseudosarcomatous" change. *Top*: Low magnification shows a hypercellular spindle cell stroma. *Bottom*: High magnification shows minimal atypia and an absence of mitotic activity. The lesion mimics low-grade endometrial stromal sarcoma, but the stromal cells lack the intimate relationship to small blood vessels characteristic of low-grade stromal sarcoma.

Clomiphene Citrate

Clomiphene citrate is an orally active nonsteroidal compound that is structurally similar to diethylstilbestrol (DES) and binds to estrogen receptors. Clomiphene reduces the number of estrogen receptors in the hypothalamus by inhibiting the process of receptor replacement, thereby stimulating the hypothalamus to respond as if estrogen levels were low by secreting gonadotropin-releasing hormone, which leads to pituitary secretion of FSH and LH. When clomiphene is used to induce ovulation, the endometrium usually displays histologic changes reflecting a hypoestrogenic state, presumably related to competitive binding of clomiphene to estrogen receptors. Based on a review of 710 biopsies, Benda found that clomiphene induced specific alterations in secretory endometrium, including a reduction in the gland/stroma ratio and a decrease in size and tortuosity of the glands.[17] Secretory activity and stromal decidualization were diminished. Sereepapong et al. also reported a similar diminution in gland density and diameter.[243] Deligdisch reported a dyssynchrony in glandular–stromal maturation

with the glands appearing consistent with a date about 7 days earlier in the menstrual cycle than the stroma.[64] Not all studies have shown consistent effects on secretory development.

Gonadotropin-Releasing Hormone Agonists

Gonadotropin-releasing hormone agonists (*GnRH*) are used mainly to suppress the endometrium before resectoscopic ablation or to decrease the size of leiomyomas before myomectomy. After GnRH treatment the endometrium becomes markedly atrophic.[27] GnRH is sometimes combined with progestins, which results in secretory changes.[150]

Human Menopausal Gonadotropin/ Human Chorionic Gonadotropin

Human menopausal gonadotropin (*hMG*) (Pergonal) and *chorionic gonadotropin* (*hCG*) have been used to treat infertile, anovulatory women with polycystic ovarian disease. The two hormones used together enhance the LH surge after initial treatment with clomiphene. The histologic effects on the endometrium are unclear. Some studies have reported retarded secretory maturation,[37,220] whereas others have described more highly developed secretory changes than expected for the chronologic date of the cycle.[89,244] There are no specific morphologic changes that can be correlated with the effects of these hormones.

Emergency Contraceptives and Abortifacients

Emergency contraceptives include high-dose estrogens, danazaol, levonorgesterel, IUD insertion, combined estrogen and progesterone (Yuzpe regimen), and mifepristone (RU-486).[109] Assessing the efficacy of emergency contraception is difficult because the percentage of pregnancies prevented by an intervention can only be approximated. Available data on the histopathologic changes induced by emergency contraceptive measures are limited. Although posttreatment endometrial samples are rarely submitted for pathologic diagnosis, it is important for pathologists to distinguish normal gestational changes and organic pathology from treatment effects. Currently, high-dose estrogen therapy and danazol are rarely used because of the unacceptable side effects for the former and contraceptive failures in the latter.

The Yuzpe regimen consists of two doses of combined pills, typically consisting of 100 μg ethinyl estradiol and 1 mg norgestrel, administered within a 12-hour interval.[315] It is estimated that this treatment prevents 74% of pregnancies, effectiveness declining as the postcoital interval lengthens. Nausea and vomiting are frequent compared to treatment with mifepristone, which is now approved for use in the United States. Proposed mechanisms of action for the Yupze regimen include inhibition of ovulation, disruption of endometrial maturation, producing an unfavorable environment for implantation, and alteration in the expression of hormone receptors or other molecules required for implantation. The effect of the Yuzpe regimen on endometrial histopathology has been assessed in several small investigations with slightly different study designs. Some investigators have reported little or no specific histologic change, whereas others have reported dyssynchronous maturation of glands and stroma.[155,217,273] In one study using a masked histopathologic review, glandular–stromal discordance for dates was not identified and the only significant difference between treated women and controls was an increase in supranuclear vacuoles in endometrial glands.[217] Other findings in this study included a reduction in MUC-1 expression (normally present in midsecretory endometrium), an increase in estrogen receptor expression, low luteal-phase serum estrogen, and reduced endometrial thickness.

Mifepristone is a synthetic steroid that produces a high-affinity progesterone receptor blockade. Mifepristone is approved for use as a single-dose *abortifacient*.[189] Mifepristone may also have utility as a contraceptive agent and, possibly, as a treatment for endometrial hyperplasia.[36] The ability of RU-486 to inhibit endometrial glandular proliferation is paradoxical, suggesting a dose-dependent antiestrogenic effect in addition to progesterone inhibition. Histologic alterations ascribed to RU-486 include inhibition of secretory activity, acceleration of degenerative changes in glandular epithelium, alteration of stromal blood vessels, and an increase in stromal mitoses.[36,152,265,272] Ultrastructural studies suggest that RU-486 inhibits the development of the nucleolar channel system and mitochondria, which are typical changes found in postovulatory endometrium.[70]

Prostaglandins

Endometrial production of *prostaglandins* increases through the secretory phase. Primary dysmenorrhea is thought to be caused by myometrial contractions induced by prostaglandins, which may account for the association between dysmenorrhea and ovulatory cycles. This mechanism could explain the beneficial effect of oral contraceptives on primary dysmenorrhea because oral contraceptives produce

endometrial atrophy and thereby reduce prostaglandin levels. The morphologic effects of prostaglandins on the human endometrium have not been well described. In rats, prostaglandins appear to induce decidualization.[274–276]

Effects of Intrauterine Devices

The histologic effects of *IUDs* on the endometrium are device specific. Plastic devices induce a focal inflammatory response (Fig. 10.30) composed of polymorphonuclear leukocytes, lymphocytes, plasma cells, macrophages, and, rarely, foreign body giant cells.[183,184,200] A significant degree of chronic inflammation is observed in 25–40% of IUD users and may be related to the duration of use.[200] Other findings include squamous metaplasia and premature predecidualization, which may represent a reaction to injury.[200,307,308] The endometrium immediately beneath the device may show pressure atrophy and focal fibrosis, whereas surrounding regions are unaffected. Inflammatory reactions occur slightly less frequently with copper-containing devices. Leukocytes are commonly confined to the gland lumens, with exudation on the endometrial surface and sparing of the endometrial stroma. Progesterone-impregnated devices release hormones in a slow, continuous fashion, producing a sharply localized area of decidualization immediately adjacent to the device.[164] Copper-containing devices may induce endothelial degeneration, necrosis, and formation of defects between endothelial cells and basement membranes. This effect, together with the increase in vessel density, may account for the increased bleeding associated with IUD use.[110,245]

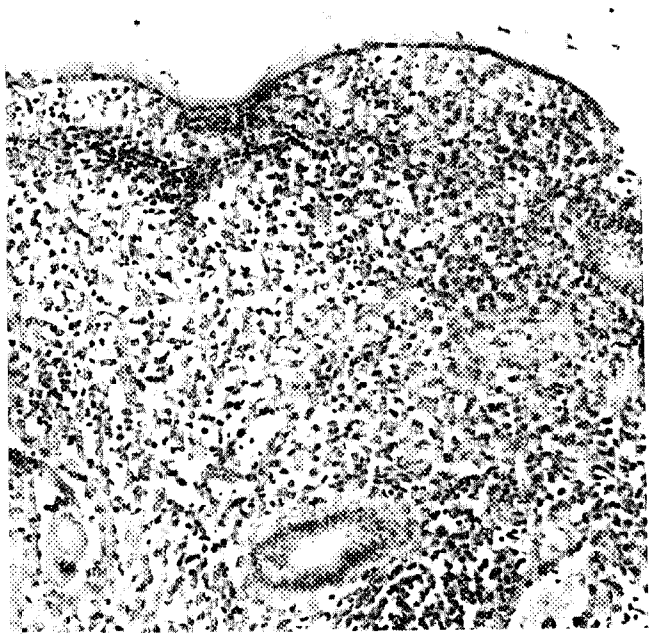

Fig. 10.30. Intrauterine device effect. Endometrium in the vicinity of an intrauterine device shows chronic inflammation.

Mechanism of Action

Three possible mechanisms proposed to explain the contraceptive effects of IUD include (1) inhibition of sperm transport from the cervix to the tube, (2) inhibition of sperm capacitation, and (3) interference with implantation.[6] Only the last hypothesis is plausibly explained by IUD-induced changes in the endometrium. For the plastic devices, the inflammatory reaction, in conjunction with an asynchronous premature decidual reaction, results in an unfavorable local environment for implantation of the blastocyst. Release of copper ions from impregnated devices may inhibit normal metabolism in endometrial cells.[205] Decidualization associated with progesterone-releasing devices may hinder implantation and render cervical mucus impermeable to sperm.

Complications

The IUD, unlike barrier methods, does not protect against sexually transmitted diseases. There is an increased risk of pelvic infection shortly after IUD insertion, probably related to the introduction of bacteria, but these organisms are cleared within 24 hours and endometrial cultures obtained 30 days after insertion are sterile.[174] IUD users may develop upper genital tract infections after this period related to sexually transmitted diseases, but these infections appear unrelated to the IUD per se[134,149] because the risk of infertility among IUD users who are monogamous is not elevated.[53] Pregnancy rates after IUD removal resemble those associated with discontinued use of other contraceptive devices.[221,235]

IUD use of any duration predisposes patients to colonization or infection with *Actinomyces*, a gram-positive anaerobic bacteria.[100] Actinomycotic infections are characterized by typical sulfur granules, composed of a dense central basophilic mass of tangled hyphae surrounded by peripheral radiating filaments (Figs. 10.31 and 10.32). The organism can be demonstrated in Papanicolaou-stained cervical vaginal smears[21] and IUD scrapings obtained after removal of the device. *Actinomyces* must be distinguished from the Splendore–Hoeppli phenomenon, a nonspecific tissue reaction, in which debris, fibrin, immunoglobulin, and complement form eosinophilic masses that may closely resemble the branching structures of *Actinomyces* but lack true filamentous bacilli.[186]

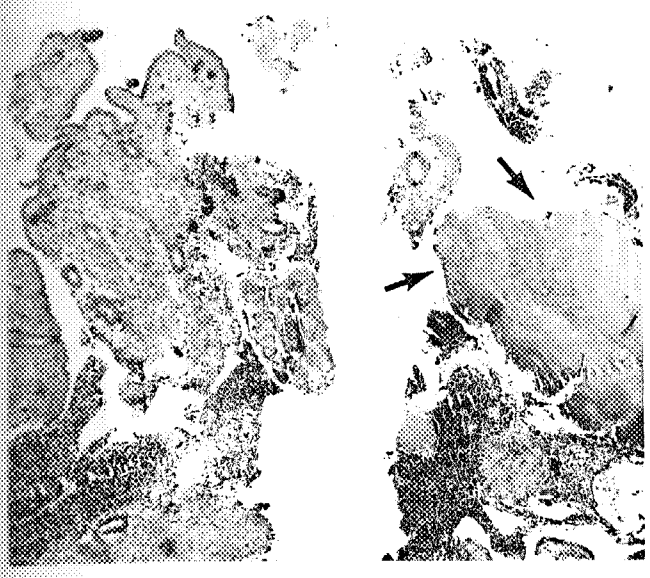

Fig. 10.31. *Actinomyces* in a patient with an intrauterine device. Sulfur granules (*arrows*) can be identified under low magnification in endometrial curettings infected with *Actinomyces*.

Actinomyces is not normally found in the cervix and vagina but is part of the normal flora of the oral cavity and gastrointestinal tract. It is likely that the organism is introduced into the lower genital tract during coitus. *Actinomyces* does not ordinarily invade mucosal surfaces, but the IUD acts as a foreign body and the associated tissue injury associated with its placement may create an anaerobic microenvironment that permits colonization by *Actinomyces* and other anaerobic organisms. Tubo-ovarian abscesses occurring in this setting tend to be unilateral.[191] However, bilateral tubo-ovarian abscesses, especially when associated with bowel or bladder involvement, may mimic ovarian carcinoma. Leukocytosis, long-term IUD use, and normal CA-125 levels provide clues to the diagnosis, and frozen section interpretation at the time of surgery may avert unnecessary procedures.[186] A serious but rare complication of the IUD is uterine perforation, with secondary involvement of the omentum and possible bowel obstruction. Copper devices produce a greater peritoneal reaction than plastic IUDs and are more often implicated in bowel obstruction. In one study, all seven copper devices that perforated into the abdominal cavity required laparotomy for removal, whereas other devices were removed laparoscopically.[203] Finally, there is a 2–3% risk among IUD users that a pregnancy will be ectopic.[274]

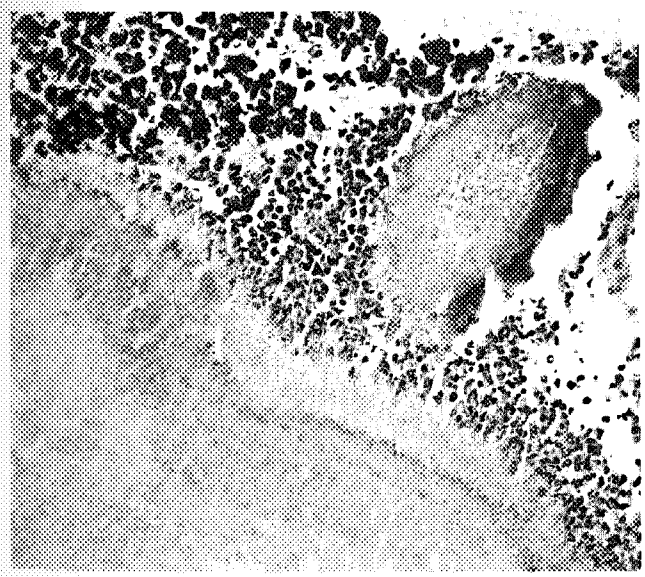

Fig. 10.32. *Actinomyces* in a patient with an intrauterine device. Sulfur granules are composed of a dense central basophilic mass of tangled hyphae surrounded by peripheral radiating filaments.

Effects of Curettage

Curettage evokes transient inflammatory and regenerative changes in the endometrium.[122] Three days after curettage, the endometrial surface consists of flattened attenuated cells. The basalis contains a serosanguinous exudate containing PMNs that clears completely in 7–9 days. In one large study, more than 83% of women had normally timed menses after a curretage, whereas in 10% it was delayed and in 7% it was early.[125,127] Eosinophilic endomyometritis following curettage has also been reported.[23,68,173] In the endometrium, the inflammatory cells form dense aggregates containing a mixed population of inflammatory cells, especially lymphocytes, whereas in the myometrium, the inflammatory infiltrate percolates through the connective tissue between muscle bundles and perivascular tissue.[68] The eosinophilic component of the infiltrate may be recruited by chemotactic factors released from mast cells in the myometrium in response to injury.[173]

Asherman syndrome is a specific posttraumatic condition associated with hypomenorrhea or amenorrhea and infertility following endometrial injury.[11,38,117,121] Inciting events include postpartum or postabortal curettage, particularly if infection is present, and more rarely, tuberculous endometritis or myomectomy. The diagnosis of Asherman syndrome is made by identifying bands of fibrous tissue or smooth muscle traversing or rarely, obliterating the endometrial cavity. Curettings obtained

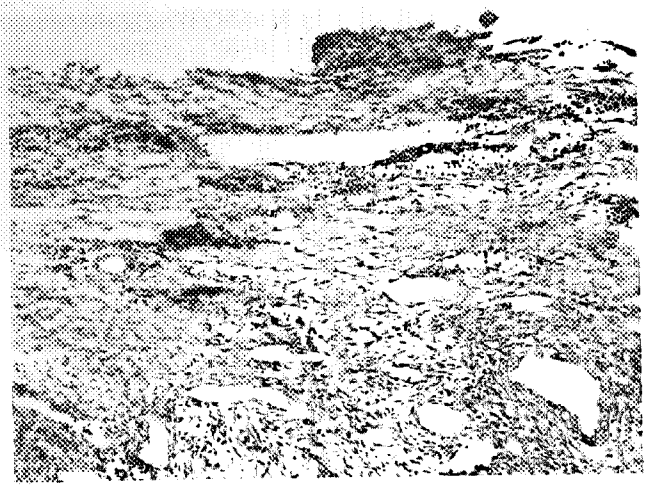

Fig. 10.33. Asherman syndrome. The endometrium is characterized by atrophy and fibrosis.

from women with Asherman syndrome usually are scant (Fig. 10.33).[79] Physiologic alterations may be severe in cases in which mild if any alterations are recognized clinically.[286] It has been postulated that the intrauterine adhesions reflect a more widespread process in which the endomyometrium is replaced by fibrous tissue.[311] Treatment of Asherman syndrome consists of curettage to break the synechiae, placement of an IUD to separate the endometrial surfaces, and cyclic estrogen-medroxyprogesterone treatment to induce endometrial proliferation.[38] This form of treatment is curative in most patients, but occasionally intrauterine adhesions recur.[286]

Effects of Laser Surgery

Endometrial ablation using the Nd:YAG laser and resection using a modified rectoscope have proven effectiveness in treating dysfunctional uterine bleeding uncontrolled by hormonal treatment.[201] Histologic descriptions of laser effects are limited and may reflect a biased subset removed for intractable bleeding.[94,218] Reepithelization of the endometrium seems to require about 3–5 months and is associated with only mild acute or chronic inflammation and foreign body giant cells surrounding carbon particles. Glandular regeneration and replacement of the endometrium by a simple cuboidal epithelium overlying a fibrous stroma or directly applied to the myometrium may be seen in the same uterus. The appearance is similar to that of Asherman's syndrome (see foregoing). Pathologic specimens obtained within 3 months of electrosurgical ablation may show necrotic myometrium, spicules of damaged muscle, florid giant cell reactions, and varying degrees of acute inflammation. After 3 months, specimens show endometrial fibrosis and a persistent giant cell reaction that may be confused with other forms of granulomatous endometritis.[50] Biopsy before treatment may be indicated to exclude the presence of hyperplasia or carcinoma.

Effects of Radiation

The morphologic changes induced by *radiation* are presented in Chapter 12, Endometrial Carcinoma, and elsewhere.[142] Briefly, cells are often enlarged, assume unusual shapes and display vacuolated cytoplasm. Nuclear changes include enlargement, pleomorphism, and hyperchromasia with poorly preserved chromatin (Fig. 10.34).

Benign Tumors

Endometrial Polyps

Endometrial polyps are benign, localized overgrowths of endometrial glands and stroma that are covered by epithelium and project above the adjacent surface epithelium. Polyps may arise from hyperplasia in the basalis because focal glandular proliferations and thick-walled feeder vessels are often identified at the base of these lesions.

Clinical Features

The prevalence of polyps in the general population is about 24%. Polyps are common in women over 40

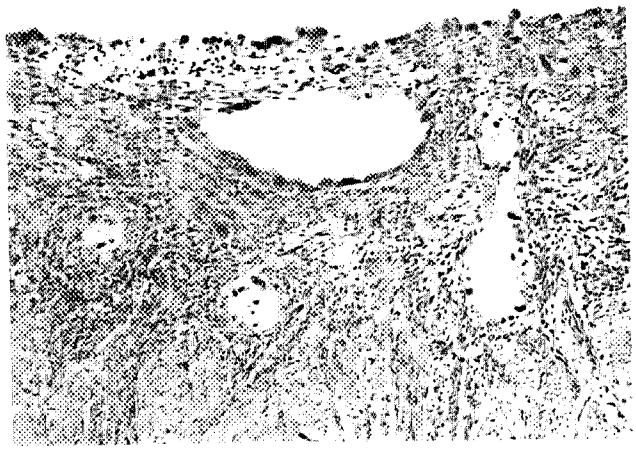

Fig. 10.34. Radiation effect. The glands and the surface endometrium are lined by cells showing nuclear atypia.

years of age and extremely rare before menarche. The most common presentations are intermenstrual bleeding or menometrorrhagia in younger women and postmenopausal bleeding in older patients. Polyps may also present as a cause of infertility.[81,290] A polyp should always be considered if abnormal bleeding persists after curettage because polyps that contain a delicate, pliable stalk may elude the curette.

Pathologic Findings

Polyps may be broad based and sessile, pedunculated, or attached to the endometrium by a slender stalk. Polyps vary in size from 1.0 mm to large masses filling and expanding the endometrial cavity (Fig. 10.35). Large pedunculated polyps may extend into the endocervical canal and project through the cervical os, producing as a visible mass on physical examination. Usually polyps have a tan, glistening surface, but irritated or infarcted polyps may appear hemorrhagic. About 20% of uteri contain multiple polyps. Polyps may originate anywhere in the uterine cavity, including the lower uterine segment, but most occur in the fundus, commonly in the cornal region. Upper endocervical polyps and mixed endometrial–endocervical polyps contain glandular epithelium from both components.

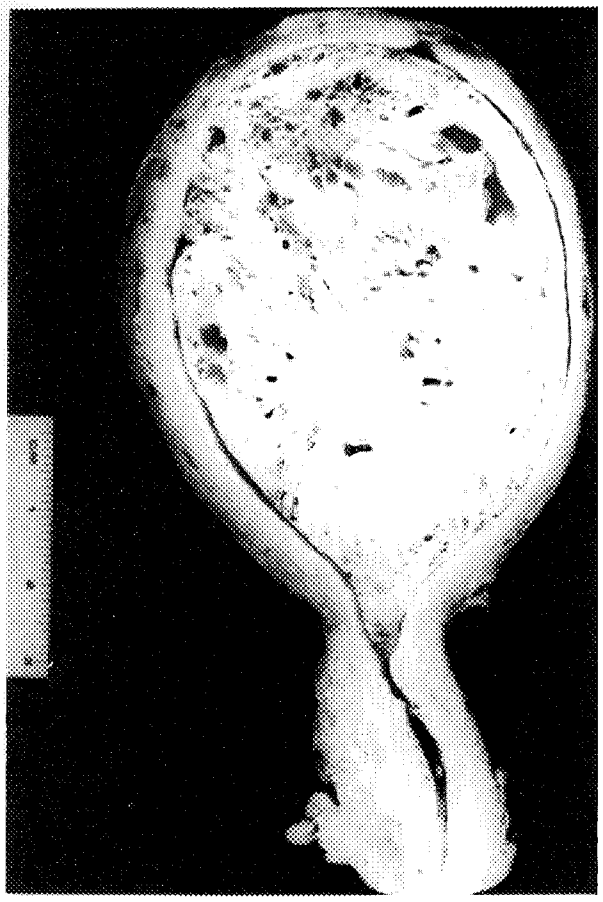

Fig. 10.35. Large endometrial polyp. The polyp entirely fills and distends the endometrial cavity.

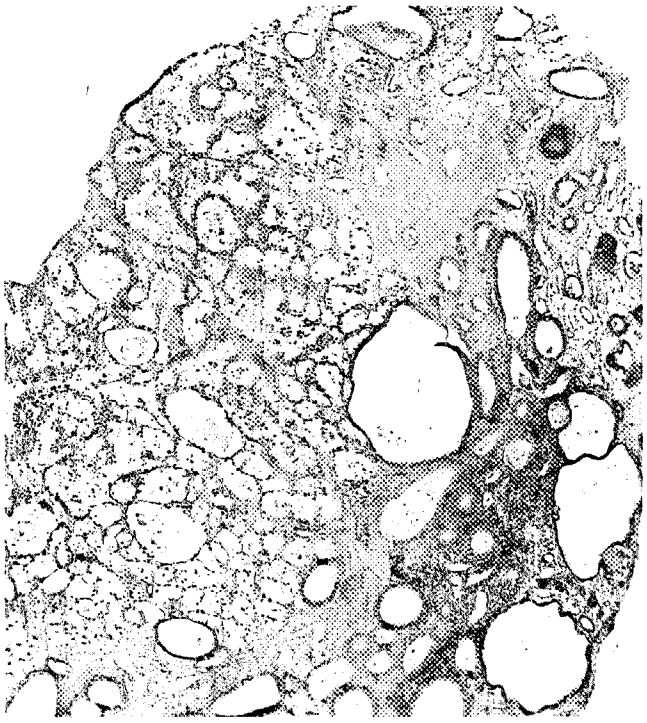

Fig. 10.36. Clear cell carcinoma in the tip of an endometrial polyp. The tumor shows a tubulocystic pattern and is confined to an endometrial polyp. (Reprinted by permission of Kurman and Scully, ref. 144.)

Glands in polyps often fail to cycle normally; secretory changes may be weak or absent in contrast to the surrounding endometrium or the glands may appear dilated and inactive. Squamous metaplasia may be present. The mesenchymal component of polyps may consist of endometrial stroma, fibrous tissue, or smooth muscle, but generally the stroma appears more fibrous than normal fundic endometrium. Decidualization is uncommon in women not receiving exogenous hormones.[103] Polyps containing a significant amount of smooth muscle are referred to as adenomyomatous. Hyperplasia, carcinoma (any type) (Fig. 10.36), and carcinosarcoma may involve or be entirely confined to a polyp.[15,67,129,144,246,249,253,298] Although the base of a polyp usually contains thick-walled vessels, abundant dilated vessels may be present, simulating a hemangioma.

Polyps are morphologically diverse lesions that are difficult to subclassify; however, most can be categorized as hyperplastic, atrophic, or functional.

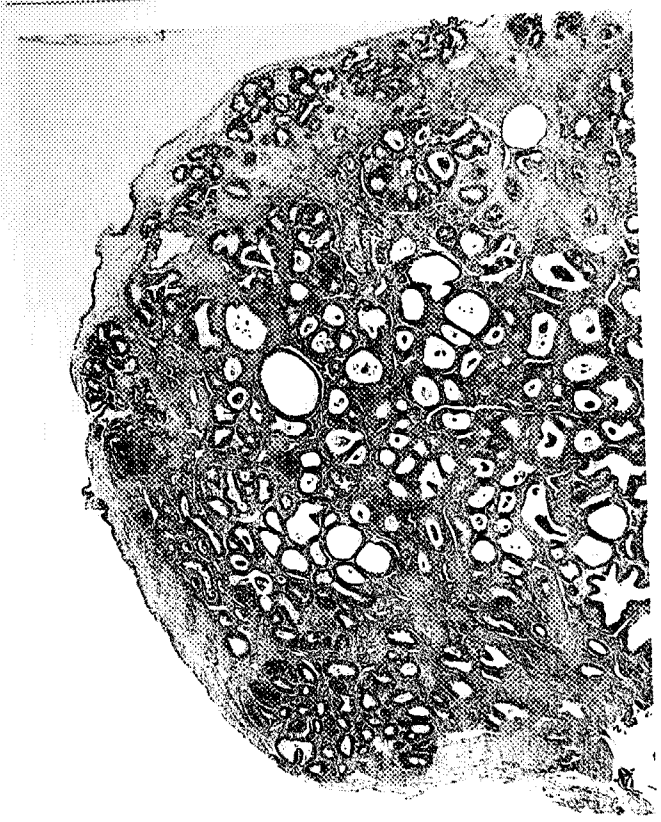

Fig. 10.37. Hyperplastic polyp. The polyp is broad based and composed of irregularly shaped, crowded, hyperplastic glands.

Hyperplastic polyps contain proliferating, irregularly shaped glands resembling diffuse, nonpolypoid endometrial hyperplasia (Figs. 10.37 and 10.38). These polyps, like diffuse endometrial hyperplasia, are probably etiologically related to hormone imbalances. There is no evidence that these have the same significance as diffuse hyperplasia, however, so it is generally best to avoid the subcategorization, i.e., hyperplastic, in the diagnosis. Atrophic polyps consist of low columnar or cuboidal cells lining cystically dilated glands. These polyps are typically found in postmenopausal patients and may represent regression of hyperplastic or functional polyps. Functional polyps containing glands resembling normally cycling endometrium are relatively uncommon (Fig. 10.39).

Polyps may be difficult to recognize in curettage specimens.[166,316] Ideally, they appear as polypoid-shaped fragments of tissue, with epithelium on three sides. However, these criteria may be difficult to appreciate if lesions are fragmented or partially removed. In addition, normal endometrium has an irregular surface that may appear as a polypoid fragment with epithelium on three sides when sectioned tangentially; therefore, identification of finger-like tissue fragments alone is insufficient for diagnosis. Identification of tissue fragments containing irregular glands, dense or fibrous stroma (Fig. 10.40), or thick-walled vessels that contrast with the appearance of the surrounding endometrium suggest a polyp. However, these criteria should be appreciated in tissue fragments lined with attached surface epithelium because normal basalis can show some of these features. Molecular studies have demonstrated that polyps are clonal and may contain abnormalities on chromosome 6.[58,59,261]

Differential Diagnosis

The differential diagnosis of polyps includes hyperplasias, polypoid adenocarcinomas, adenofibromas, and adenosarcomas. Florid hyperplasias may mimic polyps because they can assume a polypoid configuration; however, these are diffuse abnormalities that should involve most or all fragments in a specimen, whereas true polyp fragments generally com-

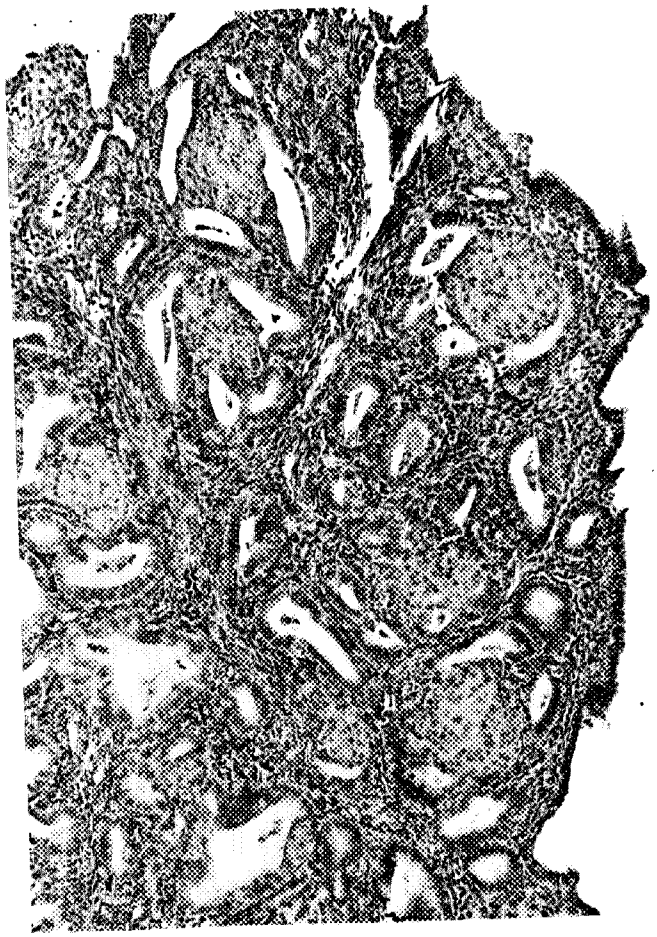

Fig. 10.38. Hyperplastic polyp. This polyp contains crowded irregular glands, some of which show squamous change.

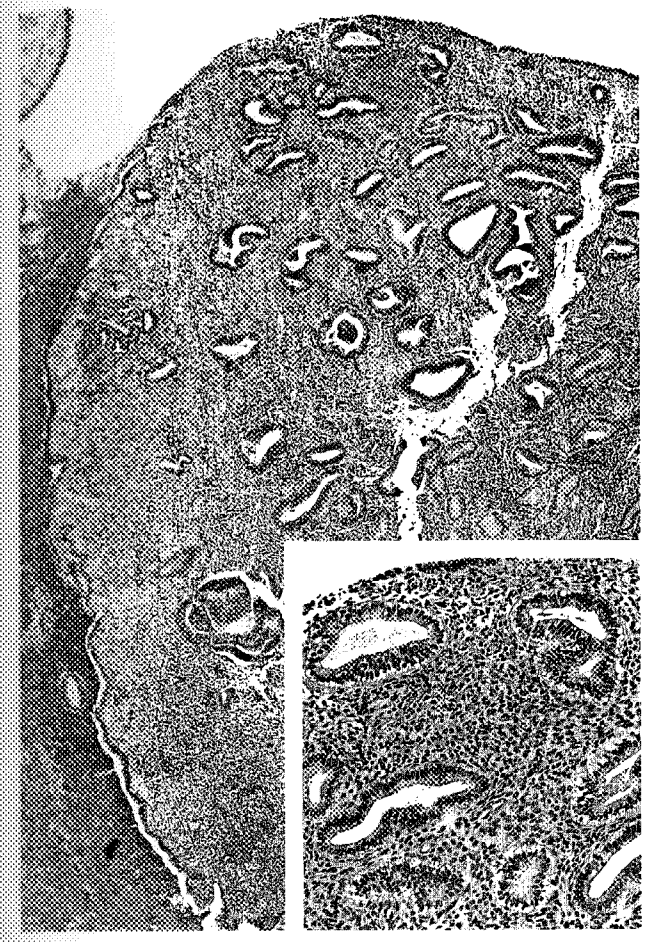

Fig. 10.39. Functional polyp. This polyp contains secretory glands surrounded by dense stroma. *Inset*: Secretory glands with subnuclear vacuoles.

prise only a portion of such tissue. Adenocarcinomas with polypoid growth will retain diagnostic features of malignancy. Adenosarcoma is distinguished from a benign polyp because the stromal cells demonstrate increased mitotic activity, cytologic atypia, and a tendency to encircle glands. Preserved fragments of adenosarcoma may display a characteristic leaflike pattern at low magnification that would not be found in a typical benign polyp (see Chapter 13, Mesenchymal Tumors of the Uterus).

Clinical Behavior and Treatment

At most, 5% of polyps contain carcinoma; however, 12%–34% of uteri containing endometrial carcinoma also contain a polyp.[210,234] A long-term prospective study of patients with endometrial polyps found that endometrial carcinoma ultimately developed in 3.5% of the patients, but nearly one-half the women who developed carcinoma had been treated with intracavitary radium.[10] Polyps may represent a marker of increased cancer risk because they reflect a tendency for the endometrium to develop proliferative lesions. However, there is no evidence to suggest that polyps themselves have a significantly greater propensity for developing carcinoma than adjacent endometrium. In general, polyps containing atypical hyperplasia or carcinoma should be treated similarly to comparable flat lesions. Polyps containing lesser degrees of hyperplasia are often treated by polypectomy and curettage. In young women with atypical hyperplasia or carcinoma confined to a polyp, polypectomy can be considered as a treatment to preserve fertility, provided that the entire endometrial cavity has been vigorously curetted (hysteroscopically confirmed) and the nonpolypoid endometrium appears normal. Endometrial intraepithelial carcinoma (EIC), the presumed precursor of serous carcinoma, may be identified as a malignant surface change in atrophic polyps removed from elderly women.[246,298] Staging should be

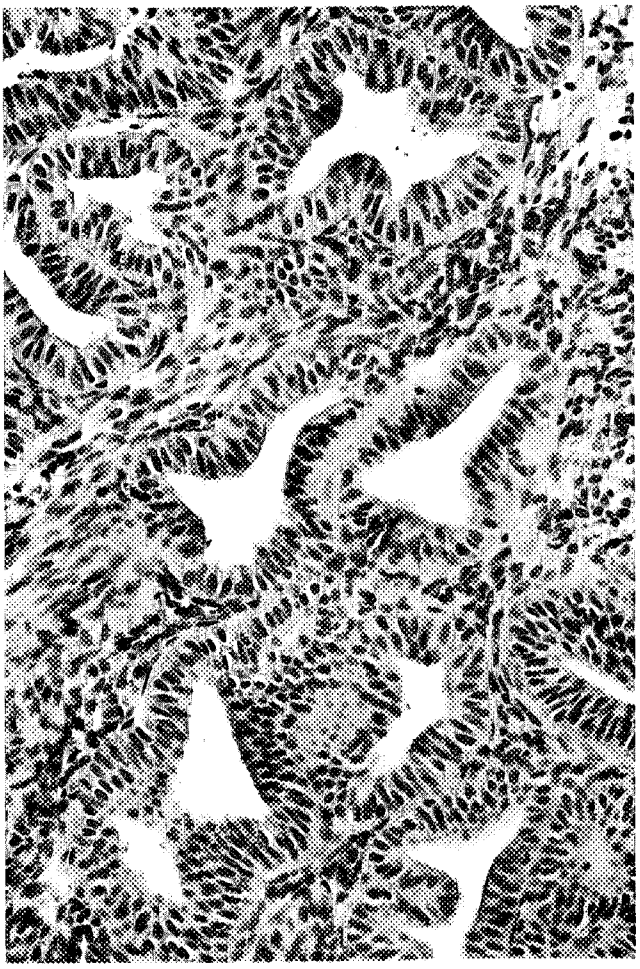

Fig. 10.40. Endometrial polyp. The stroma of a polyp typically is fibrotic.

considered for all women with EIC or small amounts of serous carcinoma in the uterus ("minimal uterine serous carcinoma") because some of these patients have disseminated disease.[298]

Atypical Polypoid Adenomyoma

Atypical polypoid adenomyomas (*APA*) are typically detected during the reproductive and perimenopausal period. In a series of 55 cases, Longacre et al. reported that 96% of patients were premenopausal with a median age of 39 years.[157] Among patients with complete histories, 28 were nulliparous, 15 had a history of infertility, and 13 were obese, suggesting that these lesions may share risk factors with type I endometrial carcinomas. The lesion has also been reported in patients with Turner's syndrome who have been on estrogen replacement therapy.[46] APAs, like other polyps, usually present with abnormal uterine bleeding.

The APA grossly resembles a typical endometrial polyp (Fig. 10.41) and often involves the lower uterine segment. Microscopically, the APA is composed of irregularly shaped hyperplastic glands arranged haphazardly within stroma containing abundant smooth muscle[165] (Fig. 10.42). Extensive morular squamous metaplasia, sometimes showing central necrosis, may exaggerate the appearance of glandular crowding and raise concerns regarding the possibility of carcinoma. The glandular cells display nuclear atypia, loss of polarity, and cytoplasmic eosinophilia (Fig. 10.43). The smooth muscle is arranged in short interlacing fascicles, rather than elongated muscle bundles typical of normal myometrium. The lesion may be difficult to identify in curettings and must be distinguished from hyperplasia, infiltrating carcinoma, or a malignant mixed mesodermal tumor. The focal nature of APA and the intimate admixture of smooth muscle and glands distinguish this lesion from atypical hyperplasia (see Chapter 11). In contrast to adenocarcinoma, desmoplastic reactive stroma resembling chronically inflamed granulation tissue is not found (see Chapter 12).

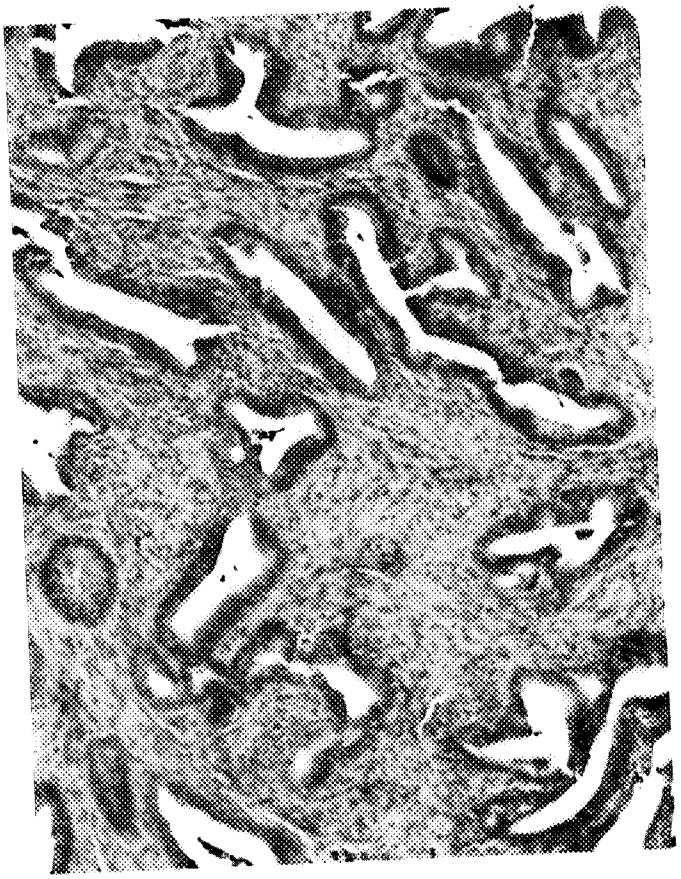

Fig. 10.42. Atypical polypoid adenomyoma. Large and atypical glands are surrounded by smooth muscle. (Reprinted by permission of Mazur, ref. 165.)

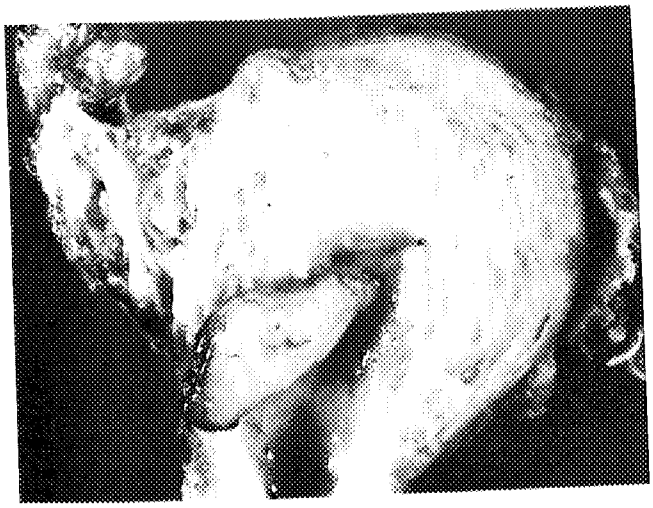

Fig. 10.41. Atypical polypoid adenomyoma. The lesion is a discrete pedunculated polypoid mass within the uterine cavity.

Compared to most APAs, carcinomas generally show greater cytologic atypia and more glandular crowding and architectural complexity. Because myometrial invasion is rarely demonstrable in curettings of carcinoma, the diagnosis of APA should be strongly considered whenever atypical glands surrounded by obvious bundles of smooth muscle on routine stains are identified. However, studies demonstrate that the stroma in these lesions contains a mixture of smooth muscle cells, fibrous tissue, and endometrial stroma, which has prompted some authors to propose the alternative term *atypical polypoid adenomyofibroma* to emphasize the stromal heterogeneity.[157,258] Furthermore, immunohistochemical studies have demonstrated that the stroma in APA and adenocarcinoma may show sim-

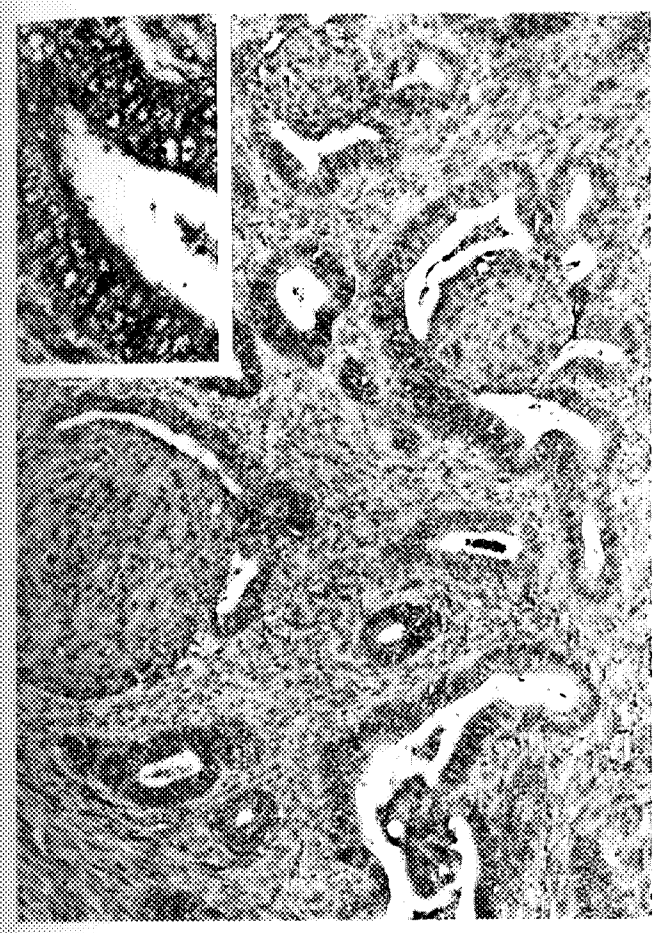

Fig. 10.43. Atypical polypoid adenomyoma. The lesion contains irregular glands with foci of squamous differentiation. Smooth muscle surrounds the glands. *Inset*: Cytologic atypia is characterized by enlarged nuclei with prominent nucleoli.

ilar markers including smooth muscle actin, desmin, and CD 34, underscoring the possible limited utility of these stains in differential diagnosis. Squamous cells with mild atypia can be found in both adenocarcinomas and APA (Fig. 10.43); therefore, this feature is not helpful in separating these entities. Another related differential diagnosis is uterine adenomyoma, a lesion composed of glands and stroma consisting predominantly of smooth muscle with a minor component of endometrial stroma. The glands usually resemble proliferative endometrium but may show focal dilatation, mucinous, tubal or squamous differentiation. Because the endometrial stroma tends to encircle the glands, these lesions may be confused with adenosarcoma. However, atypia and mitoses are generally not identified in these stromal cells. The smooth muscle component may be cellular or demonstrate occasional mitoses.[91]

In rare instances, it may not be possible to distinguish an APA from a well-differentiated carcinoma, and a hysterectomy will be necessary. Based on data suggesting that APAs with marked architectural complexity have an increased tendency to recur following conservative treatment and may be associated with invasive carcinoma, Longacre has proposed designating these lesions as *low malignant potential*. Although the smooth muscle in APA may show some mitotic activity (generally less than two mitoses per 10 high-power fields), the cytologic atypia and more frequent mitoses found in malignant smooth muscle are not seen (Chapter 13, Mesenchymal Tumors of the Uterus).[157] APA is a benign lesion that can be cured by curettage, permitting premenopausal women to preserve their fertility and become pregnant.[165,314] However, Longacre reported that 45% of lesions treated conservatively recurred clinically, although none progressed to a fatal invasive carcinoma. APAs associated with adenocarcinoma have been rarely reported, and criteria used for the diagnosis of carcinoma presented here should be applied, recognizing that the majority of errors in this area result from overdiagnosis.[175,266,270]

Teratoma

Primary benign teratomas of the uterus are extremely rare,[146,163,278] and immature teratomas are even more unusual.[103] Teratomas must be distinguished from more common entities such as metaplasia and implantation of fetal tissues. Therefore, sufficient sampling to exclude the presence of a remnant embryo or placental and decidual tissue is required. Most cases reported in the older literature are of dubious authenticity. Nicholson concluded in 1956 that only four cases were acceptable, and since then rare additional cases have been reported.[192] Microscopically, uterine teratomas resemble those found in the ovary. Typically, these neoplasms contain squamous and respiratory-type epithelium, adipose tissue, and sebaceous glands.[163]

Brenner Tumor

An example of a *Brenner tumor* that appeared to arise from metaplasia of the uterine serosa and involved the subjacent myometrium has been described.[9] Brenner tumors have also been identified in paracervical tissue.

Papillary Serous Tumor

Small *papillary tumors* lined by tubal-type epithelium resembling ovarian serous surface tumors may occur in the endometrium (Fig. 10.44). The rare cases that we have seen behaved in a benign fashion.

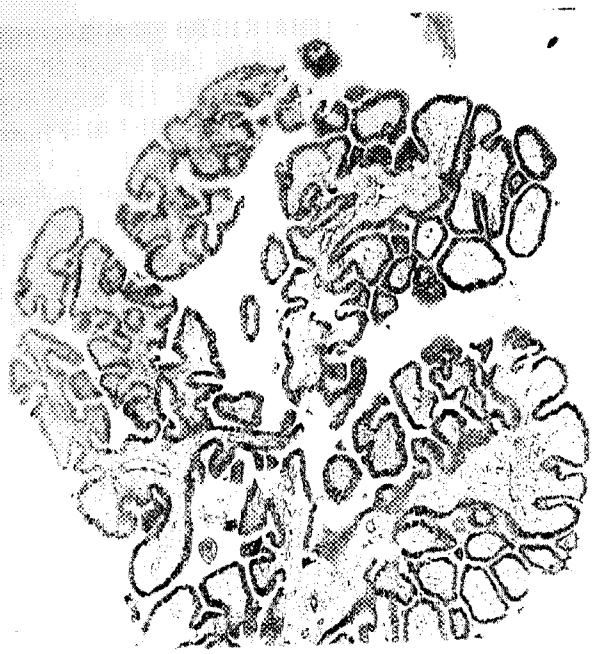

Fig. 10.44. Benign serous tumor. The lesion is composed of papillary fronds lined by bland-appearing tubal-type epithelium. The lesion resembles a serous surface tumor of the ovary.

Miscellaneous Lesions

Inflammatory Pseudotumor

Inflammatory pseudotumor, also referred to as *plasma cell granuloma* or *inflammatory myofibroblastic tumor*, are uncommon lesions that are generally viewed as non-neoplastic proliferations that may simulate neoplasms in many different organs. Uterine lesions are particularly uncommon.[92] These lesions may contain bland spindle cells representing fibroblasts or myofibroblasts, resulting in a leiomyoma-like appearance. Studied examples have demonstrated immunoreactivity for actin and vimentin and ultrastructural features of myofibroblasts. Mitotic figures are rare. A marked inflammatory infiltrate composed mainly of plasma cells with large numbers of PMNs and small and large lymphocytes is usually present. Eosinophils and mast cells may also be present. Two reported patients with uterine lesions were alive and well after 4 years of follow-up.[92]

Postoperative Spindle-Cell Nodule

Postoperative spindle-cell nodules are composed of dense proliferations of spindle cells, small blood vessels, and inflammatory cells, representing an exuberant reparative response at a site of injury. The high level of mitotic activity may raise the differential diagnosis of sarcoma, but cytologic atypia is lacking. This lesion is more common in the vagina (see Chapter 4, Diseases of the Vagina) but has been described in the endometrium[46] (see Chapter 13, Mesenchymal Tumors of the Uterus).

Lymphoma-Like Lesion

A *lymphoma-like lesion* characterized by aggregates of large lymphoid cells with only rare plasma cells and PMNs has been described in the cervix (see Chapter 6, Benign Diseases of the Cervix).[313] The aggregates of lymphoid cells resemble reactive germinal centers but lack a peripheral layer of mature lymphocytes. The large lymphoid cells include cleaved and noncleaved follicular center cells and immunoblasts. A mixed inflammatory infiltrate is present at the periphery of the aggregates. Typically, the lesions arise on a background of chronic endometritis. The polymorphism of the infiltrate with associated germinal centers, the background of chronic endometritis, and the absence of a gross mass assist in the distinction of this lesion from a true malignant lymphoma (see Chapter 13, Mesenchymal Tumors of the Uterus).

Massive Lymphocytic Infiltration in Leiomyomas

Massive lymphocytic infiltration in leiomyomas has been reported.[76] In addition to a moderate to dense infiltration of small lymphocytes, plasma cells, rare eosinophils, and occasional germinal centers are present. The inflammatory process does not involve the endometrium and adjacent myometrium. The underlying cause of this condition is unknown, and the patients reported were apparently disease free after 12 years of follow-up. The gross and microscopic findings of this lesion distinguish it from lymphoma. In contrast to a lymphoma, which is soft, fleshy, and poorly circumscribed, a leiomyoma with a dense lymphocytic infiltrate has the gross appearance of a typical leiomyoma, being firm and well circumscribed. Microscopically, the leiomyoma is associated with an infiltrate containing small lymphocytes, plasma cells, and occasionally eosinophils, whereas uterine lymphomas are typically composed of large monomorphous atypical cells.

Langerhans' Cell Histiocytosis

Langerhans' cell histiocytosis can either involve the female genital tract as part of a systemic disease or be limited to the genital tract. The endometrium is rarely involved; the vulva is the most common site of genital tract involvement.[12] The lesion is characterized by clusters and sheets of Langerhans' cells with grooved and folded vesicular nuclei. There is no correlation between the clinical presentation, ex-

tent of involvement, histologic appearance, and outcome of the genital lesions, which may undergo complete regression, persistence, or recurrence.

Intravascular Menstrual Endometrium

Occasionally, menstrual detritus consisting of clusters of epithelial and/or spindle cells can be identified in uterine and parametrial blood vessels. The benign appearance of the cells distinguishes this finding from intravascular tumor.[13]

Giant Cell Arteritis

Giant cell arteritis typically is a localized process with clinical consequences reflecting the site of organ involvement. The uterus was involved in 12 of 17 cases involving the female genital tract in one report.[162] Systemic disease was identified in 11 of these patients, and 6 did not have systemic symptoms. Uterine lesions are most common in postmenopausal women and are asymptomatic. Microscopically, large numbers of vessels show narrowing and complete obliteration of the lumens by a marked inflammatory infiltrate. The inflammatory infiltrate is sharply localized to the blood vessels and consists of epithelioid histiocytes, lymphocytes, eosinophils, occasional neutrophils, and giant cells (Fig. 10.45). Fibrinoid necrosis is not identified. Asymptomatic patients with no laboratory abnormalities may not require treatment, but steroids may help symptomatic patients.[156] In contrast to giant cell arteritis, acute necrotizing arteritis in the female genital tract is characterized by fibrinoid necrosis, a more acute inflammatory infiltrate, and an absence of giant cells. Isolated necrotizing arteritis is usually an incidental finding characterized by small- and medium-sized arteries demonstrating fibrinoid necrosis associated with mononuclear infiltrates and rare PMNs. Immune complexes are demonstrable using immunohistochemistry in many cases. The lesion is most common in the cervix but can occur anywhere in the genital tract. Possible etiologies of the lesion include a drug reaction, a response to a foreign body, and an immune reaction to vessels following injury. Patients may present with menorrhagia or postmenopausal bleeding. A systemic vasculitis should be excluded clinically.[82]

Arteriovenous Malformations

Uterine arteriovenous malformations are vascular fistulas composed of an admixture of arterial, venous, and capillary-like channels involving the myometrium and sometimes the endometrium. These lesions may be either congenital or acquired.[78] Although most are considered to represent hamartomas, many patients have had a prior curettage,

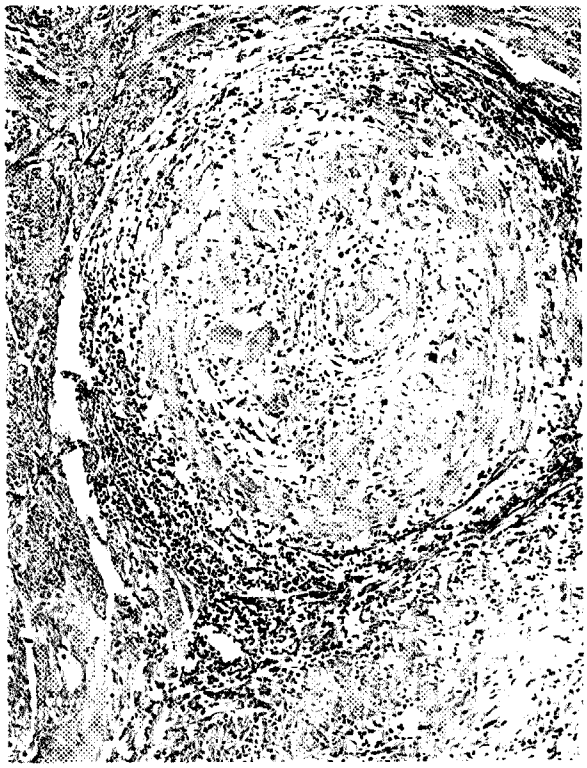

Fig. 10.45. Giant cell arteritis. Marked chronic inflammatory infiltrate consisting mainly of lymphocytes with scattered giant cells involving an artery.

suggesting a possible etiologic relationship to this procedure. These lesions usually present in adults with heavy vaginal bleeding. Curettage does not successfully control the hemorrhage and may in fact result in exacerbation of the bleeding. Clinical examination is generally unrevealing, but pelvic angiography or ultrasonography can facilitate the diagnosis. Microscopically, the lesions may be circumscribed or diffuse in the myometrium with or without endometrial involvement. Arteriovenous malformations are composed of a varying proportion of thick- and thin-walled vessels. The thick-walled muscular vessels often show fibrous intimal thickening and represent both arteries and veins. Lesions may erode into the endometrium, producing an obvious source of bleeding, but in some cases with minor bleeding the malformation is entirely intramural. Hysterectomy usually is necessary to control bleeding, although some cases have been managed successfully by intra-arterial embolization.[213]

Heterologous Tissues

Heterologous tissues including bone,[52,88,90,115,190] cartilage,[1,90,190,227] smooth muscle,[22] and glial tissue[190,193,223,318] have been reported in the endometrium. Two theories advanced to account for

the presence of these tissues include metaplastic transformation of the endometrial stromal cell and implantation of fetal tissue after abortion and instrumentation, with the fetal tissue persisting and growing as a homograft. Before classifying heterologous tissue as benign, the pathologist should exclude the possibility that the tissue in question is not a deceptively bland-appearing component of a malignant mixed mesodermal tumor or an adenosarcoma. Heterotopic bone in the endometrium is characteristically found in women with a history of repeated abortions and endometritis.[52,88,115,190] In rare instances, the bone may represent metaplasia of the endometrial stroma, triggered by inflammation. In most cases, the association with prior pregnancy, the immaturity of the heterologous element, and the rarity of osseous metaplasia in other types of endometritis indicate that it represents implantation from fetal parts.

Heterotopic cartilage in the endometrium (Fig. 10.46) frequently is associated with a history of prior abortion and is, therefore, caused by implantation of fetal tissue.[190] A few patients have no history of pregnancy and, furthermore, in the series reported by Roth and Taylor[227] one of the patients was 52 years old. Microscopically, the cartilage was mature, and a transition from endometrial stromal cells to chondrocytes was found in some, suggesting a metaplastic process. Smooth muscle is only considered

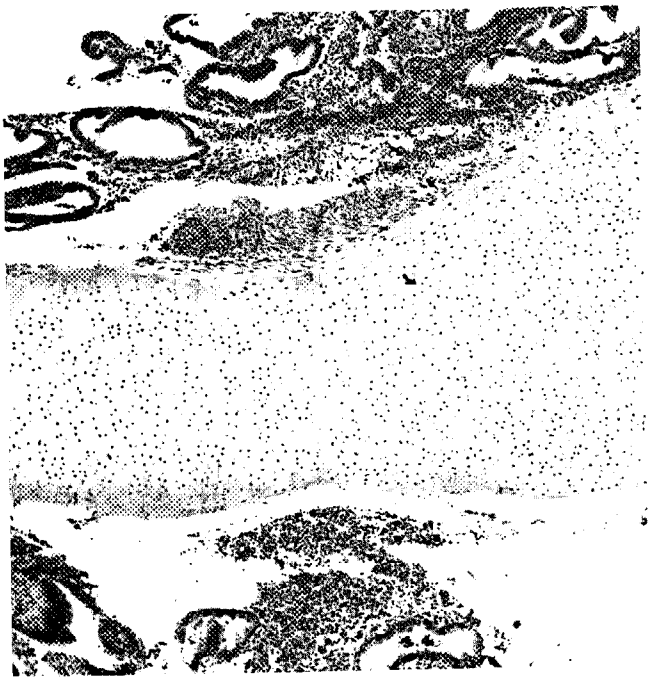

Fig. 10.46. Heterotopic cartilage. A well-circumscribed fragment of cartilage is surrounded by otherwise normal-appearing endometrium.

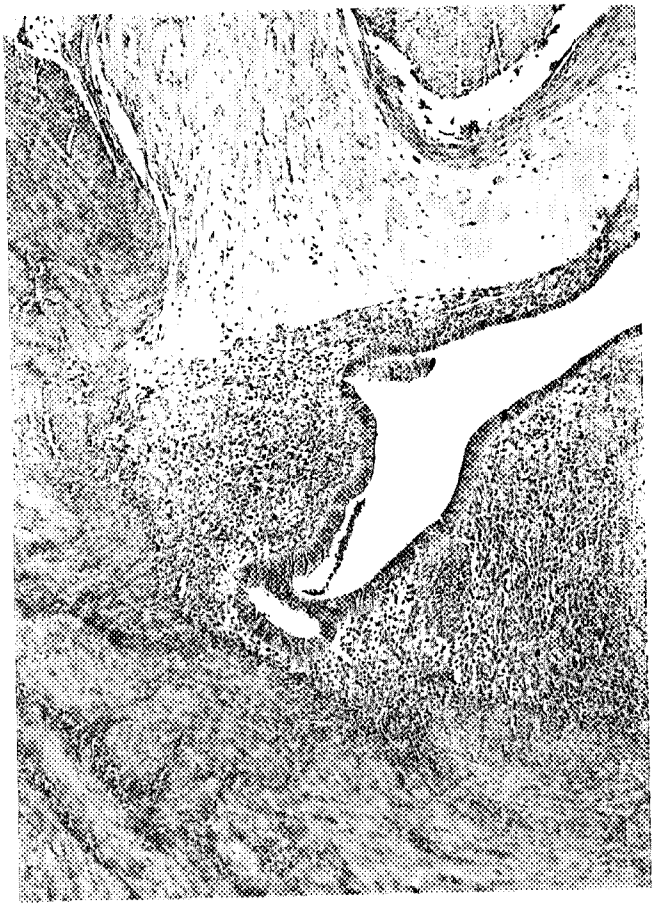

Fig. 10.47. Mature glia. A well-circumscribed glial implant is present in the *top* of the field just above an endometrial gland.

heterologous when it is localized in the endometrium. Benign heterologous smooth muscle may form fascicles or nodules within the endometrium and sometimes appears continuous with the underlying myometrium. This tissue may develop from endometrial stromal cells that have undergone metaplasia, as the two have a common anlage.[22]

The occurrence of multiple microscopic foci of mature glial tissue in the endometrium is well recognized.[46,193,223,318] These foci are composed of cells lacking mitoses and are often surrounded by a lymphocytic and plasma cell infiltrate, resembling graft rejection (Fig. 10.47). Most cases have a history of instrumented termination of pregnancy. This history, together with the unlikely development of monotypic heterologous glial tissue in the uterus, suggests that these lesions represent remnant fetal tissue. Theoretically, gliomas of the uterus may occur, and in one reported case the follow-up was uneventful.[312] Other rare heterologous tissues that have been found in the endometrium include skin, retina, skeletal muscle, liver, and kidney.[46,278] Like

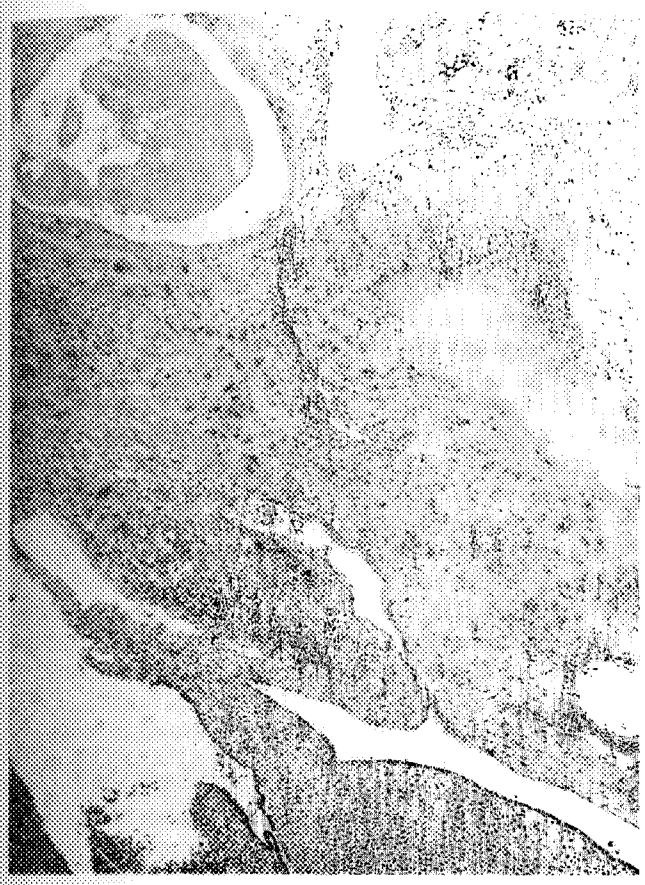

Fig. 10.48. Subinvolution of the uterus. A partially involuted placental site composed of enlarged vessels with intermediate trophoblastic cells and fibrinoid replacing the vascular walls. The underlying endometrium has enlarged, dilated glands and a decidualized stroma.

the previously described heterotopic tissues, these probably represent fetal tissue remaining after an abortion. Bone, squamous cell, and muscular metaplasia may represent underrecognized causes of infertility.[230]

Subinvolution of the Uterus

After delivery of the placenta, the uterus normally decreases dramatically in size over a period of 6–8 weeks. Failure of the uterus to return to its normal size is referred to as subinvolution. On physical examination, the subinvoluted uterus is typically enlarged to 6- to 8-week size, soft, and boggy rather than firm and normal in size. Occasionally the uterus is considerably more enlarged. Grossly, the serosa may have a slightly bluish cast. The cut surface reveals a thickened wall with enlarged blood vessels projecting from the surface. Microscopically, remnants of the placental site, containing intermediate trophoblastic cells and enlarged vessels enmeshed in eosinophilic fibrinoid along with necrotic deciduas and inflammation, are present (Fig. 10.48). A retained placental site may serve as a nidus for infection and the subsequent development of postpartum endometritis.

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